Health technology assessment of hyperphosphatemia management among hemodialysis patients in Lebanon

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CONTENT

CHAPTER 1

GENERAL INTRODUCTION

By the end of the Lebanese civil war in 1992, the healthcare system in Lebanon was at its worst. Since then, the Lebanese government has adopted a "public rehabilitation strategy" for the health sector, entailing the double objective of supporting the Ministry of Public Health in planning for health resources and services, as well as reducing health expenditures [1]. This reform has attained recognized accomplishments in terms of improving the equity and efficiency of the national healthcare system [2]. Nevertheless, the system is still striving to reconcile the two competing values of quality improvement and cost containment [3,4]. As ensuring "better health for all Lebanese" while reducing health expenditures is at the top of the national health agenda [1,3,4], there have been numerous calls for incorporating health technology assessment (HTA) to support decision making in national health care [4–6]. HTA is "a form of policy research that systematically examines short- and long-term consequences, in terms of health and resource use, of the application of a health technology" [7]. HTA aims to provide input to decision making in policy and practice [7], and employs economic evaluations as a core component of this process [8].

This dissertation aims to explore the HTA of hyperphosphatemia management among hemodialysis patients, with a focus on the Lebanese setting. We open this ***First Chapter*** with an overview of the burden of hyperphosphatemia among hemodialysis patients. We then display current knowledge related to the economic considerations of phosphorus-lowering interventions. We present, thereafter, the current situation in Lebanon in terms of managing hemodialysis patients, HTA and economic evaluations. We conclude with the objectives and outline of the dissertation.

HYPERPHOSPHATEMIA: A HEAVY CLINICAL AND ECONOMIC BURDEN

Chronic Kidney Disease (CKD) is a general term for heterogeneous disorders affecting the structure and function of the kidney, leading to sustained kidney damage and/or a decreased level of kidney function [9,10]. As the disease progresses, kidney failure develops, and associated complications become increasing risks for morbidity and mortality. This is when treatment by renal replacement therapy (RRT) becomes essential for survival [11]. RRT modalities include in-center hemodialysis, home hemodialysis, peritoneal dialysis, and kidney transplantation. Despite the increasing use of kidney transplantation (especially in Nordic countries, numerous other European countries, some Arab Gulf countries, and Canada, etc.) and home hemodialysis (especially in Australia and New Zealand) [12], in-center hemodialysis remains the main RRT worldwide [12–15]. Hemodialysis is a method for clearing waste products and removing excess fluids from the body [16]. Using an artificial kidney, the blood from the patient circulates through a dialyzer, where waste products are removed by diffusion and fluids by ultrafiltration. Cleared blood is then returned to the patient with the assistance of a pump and tubing [17]. RRT is unable to reverse kidney damage, and renal failure is often coupled with a loss of the excretory, regulatory and endocrine functions of the kidney, leading to complications in almost every organ system [18]. Specifically, the progression of renal disease is accompanied by a disturbance of the normal homeostasis of phosphorus, mainly due to the imbalance of the bone metabolic axis and the inability of the damaged kidneys to excrete phosphorus load. These changes lead to a positive phosphorus balance and subsequently elevated serum phosphorus level, i.e. hyperphosphatemia [19]. The latter is a well-established risk factor for morbidity and mortality [20–25], and is labeled "the silent killer of hemodialysis patients" [26]. Hyperphosphatemia is also linked to increased all-cause, cardiovascular, and fracture-related hospitalizations [27,28]. Moreover, it is associated with higher odds of pruritus, poor sleep quality [23], bone pain and deformities, muscle pain and weakness [29,30], calciphylaxis [31], decreased physical functioning [32], as well as greater prescription of medication and a higher pill burden [33,34], resulting in significant cost implications for healthcare systems [27,33,35,36], and a lower quality of life (QOL) for affected patients [34,37].

Accordingly, adequate serum phosphorus control is a key aim of treatment approaches for possibly reducing health-related complications [9,10], and improving patients' QOL and longevity [37]. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) [9] guidelines recommend maintaining serum phosphorus between 3.5 and 5.5 mg/dL, whereas the more recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [10] suggest lowering phosphorus levels towards the "normal" range of 2.5-4.5 mg/dL. The efficacy of these recommendations has yet to be demonstrated, as to date we lack conclusive evidence that decreasing serum phosphorus to a certain target level is associated with beneficial patient outcomes [38].

HYPERPHOSPHATEMIA MANAGEMENT: THE EVERLASTING CHALLENGE

More than a decade after the first international clinical practice guideline addressing the CKD-mineral bone disorder was issued [9], a gap still exists between the recommended and measured serum phosphorus levels of hemodialysis patients in clinical practice [39]. Hyperphosphatemia remains the most common mineral abnormality among this patient population in developed and developing countries [40,41]. With nearly 1 in 2 hemodialysis patients being hyperphosphatemic [42,43], hyperphosphatemia management is one of the most important challenges facing contemporary nephrology [44].

Hyperphosphatemia is essentially managed by a combination of three strategies: (1) hemodialysis, (2) phosphate binding medications, and (3) a low-phosphorus diet. As mentioned above, hemodialysis removes phosphorus from the blood through dialytic techniques. However, this treatment is unable to maintain a net zero balance of phosphorus [29], and typically needs to be coupled with other measures. Phosphate binders are medications that bind with phosphorus and reduce its net intestinal absorption. They are often categorized either as calcium-based, calcium-free or combination preparation agents [45]. The former two types have been studied widely. Their prescription is governed by many factors, including the side effects of the pill itself, pill burden, patient compliance, and the phosphorus content of meals/snacks, in addition to cost considerations, all of which are essential in considering the prescription of these medications [39,45]. Non-adherence to phosphate binders prevails among hemodialysis patients, ranging between 22 and 74% (mean: 51%), and is mainly driven by higher pill burden, among other factors [46,47]. Finally, dietary phosphorus restriction is the basis for achieving optimal phosphorus management, and a low-phosphorus diet has been described as the most effective means in this regard [48,49]. Nevertheless, adherence to a low-phosphorus diet is thought to be the least prevalent and the "most complicated" among all dietary restrictions required from hemodialysis patients [50]. Non-adherence rates remain exceedingly high, ranging between 19 and 57% [40,51]. Education in nutrition is an effective intervention for enhancing adherence and facilitating dietary changes among chronic patients [52]. Specifically, through systematic reviews of the literature, Matteson & Russell [53], Caldeira et al. [54] and Karavetian et al. [55] concluded that highly intense, long-term, individualized nutrition education, provided by renal dietitians and using cognitive/behavioral strategies, is effective in managing hyperphosphatemia among hemodialysis patients, without compromising their nutritional status. Patients exhibit improved adherence when dietitians provide nutritional care tailored to their medical (e.g. residual kidney function, co-morbid conditions, medications including binder therapy, serum values), dietary (e.g. food preferences and intake) and personal characteristics (e.g. culture, socioeconomic status, religious status and beliefs) [52,56–58]. This highlights the important role of a competent renal dietitian as an integral part of the multidisciplinary nephrology team. Renal dietitians are uniquely qualified to provide intensive patient education and carefully plan a well-balanced diet to maintain an optimal nutritional status and prevent the rise of serum phosphorus [10,59,60].

Hemodialysis, phosphate binders and a low-phosphorus diet have proven to be clinically effective interventions in managing hyperphosphatemia. Yet, given continually rising healthcare costs and the reality of limited budgets, cost considerations are gaining more and more attention in decision making, with regard to the adoption of health technologies [61].

HTA is the multidisciplinary field of policy analysis that encompasses the medical, social, ethical and economic implications of development, diffusion, and use of a health technology [62]. It addresses both the direct and intended consequences of a health technology, as well as its indirect and unintended outcomes, in a systematic, transparent, unbiased, and robust manner [62,63]. HTA is used to determine the relative "value for money" provided by a health technology. By acting as a bridge between the world of research and decision making, HTA aims to guide policy makers regarding the appropriate use of technology and the efficient allocation of resources [62–64]. Economic evaluations are frequently used in HTA, as an insightful tool for achieving efficiency in health care [61].

Economic evaluations compare the costs and consequences of at least two interventions (the one under study and a natural comparator). They cover a wide range of studies, including cost-effectiveness analyses (CEA), which are used if the effects are expressed in natural units, and cost-utility analyses (CUA) which are used if the intervention affects both length and quality of life. In CUA, the quality-adjusted life-year (QALY) is used as outcome [61]; this is considered as the preferred outcome in economic evaluations [65]. The role of HTA varies significantly between countries [62], and although several countries have developed systems to identify health technologies that provide the best value for money, formal HTA appears to be non-existent or limited in low- and middle-income countries, where there is evidence only of some informal HTA [66,67].

HYPERPHOSPHATEMIA MANAGEMENT: ECONOMIC CONSIDERATIONS

As mentioned above, hyperphosphatemia management among hemodialysis patients relies on adequate dialysis, phosphate binders, and a low-phosphorus diet. Hemodialysis is the most costly RRT [68,69], posing a significant financial burden on national health systems. For instance, in the US in 2014, more than $26 billion were spent on hemodialysis patients ($87,638 per patient per year, in comparison with $73,612 for peritoneal dialysis and $32,586 for renal transplantation) [70]. Coverage and reimbursement for hemodialysis treatment differ significantly between countries [71]. In numerous low-income countries, renal failure patients have no access to health insurance, which makes treatment by hemodialysis unaffordable. For example, the cost of one session of hemodialysis amounts to $100 in Nigeria, which represents twice the minimum monthly wage paid to federal government workers [72]. In contrast, treatment by dialysis is covered in most high-income countries, despite its high cost and high cost per QALY gained ($129,090) [73–75]. This is partly due to the fact that without dialysis, patients face certain death, and as a "rule of rescue," societies tend to adopt therapies that avert certain death and direct resources towards them [75,76].

Phosphate-binding agents are the most frequently prescribed medications in dialysis patients, averaging 7 to 10 pills per day (the median daily pill count is 9) [34,36,39,77]. They are first as well in terms of spending [36]; for instance, their market value exceeds $1.5 billion in the US alone [38]. Phosphate binders could cost some patients close to $1,000 monthly [51]. Yet these medications constitute a heterogeneous group in terms of cost. Although calcium-based binders are inexpensive, their efficacy and cost-effectiveness have been outweighed by concern about their elemental calcium load and its safety over the long term [48]. On the other hand, non-calcium-based binders are highly expensive. They are associated with increased public costs, creating a significant cost barrier to their use in many patients [38,78]. The cost of implementing guidelines for hyperphosphatemia management using these binders would be debilitating to health systems [35]. Accordingly, the number of published economic evaluations assessing phosphate binders has markedly increased in recent years, in an attempt to explore whether the use of these agents would provide more value for money in comparison with traditional calcium-based binders [79–87]. However, evidence regarding the comparative cost-effectiveness of these agents remains scarce, and the quality of published economic evaluations of phosphate binders is understudied. Taken the widespread use of these medications and the high cost of novel calcium-free agents, reviewing and critically appraising evidence about their cost-effectiveness is essential for identifying research gaps in this field and generating valid, reliable and transparent conclusions for policymakers and researchers.

Finally, the implementation of evidence-based guidelines for renal practice, including the adequate staffing of dietitians, is associated with decreased hemodialysis patient hospitalization and mortality [88,89]. Moreover, interventions promoting the effective control of dietary phosphorus were suggested to increase in parallel the efficacy of phosphate binders and improve the quality of care among hemodialysis patients [90]. This would imply tremendous cost savings if shown to be true [77]. Nutrition education for hyperphosphatemia management was thus suggested as a promising cost-effective intervention. Yet, to date, no rigorous economic evaluation of this intervention is available. Accordingly, given the high-quality supportive clinical evidence, the cost-effectiveness of nutrition education for hyperphosphatemia management, as provided by renal dietitians, is worthy of investigation.

MANAGEMENT OF HEMODIALYSIS PATIENTS IN LEBANON

As in many countries, renal failure is a growing public health problem in Lebanon. According to the Lebanese National Kidney Registry (NKR) [91], the prevalence of hemodialysis grew by 33% between 2007 and 2012 (from 570 patients per million people in 2007 to 700 per million in 2012), in comparison with an increase of 5% in the Lebanese population during the same period. The Lebanese Ministry of Public Health covers the cost of therapy for 55.8% of hemodialysis patients, which is reported to account for approximately 8% of its budget [91]. The rest of the patients are mainly covered by the National Social Security Fund (25%), followed by the army, the general security and the internal security forces, the employee's mutuality, and private insurance for very few patients [91]. Detailed information regarding the financial impact of hemodialysis on Lebanese society and its main drivers is still scarce.

Since hemodialysis units in Lebanon are exclusively hospital-based, hospital dietitians are in charge of the dietetic management of hemodialysis patients, and until now limited healthcare resources have inadvertently forced the decision to not have a dedicated renal dietitian for hemodialysis patients. The role of the hospital dietitian in the hemodialysis unit is neither described nor regulated by the Lebanese Healthcare Organizations Accreditation Law. Accordingly, dietetic care for hemodialysis patients is often overlooked by hospital dietitians, who are overloaded with their other administrative, food service and clinical duties. Most hospital dietitians allocate one yearly routine consultation per hemodialysis patient, in addition to brief consultations following nephrologists' consult requests [92]. This time allocation falls far below the recommended 30 minutes per patient per week (26 hours) [93]. Furthermore, Lebanese hospital dietitians exhibit poor knowledge regarding and low conformity with the implementation of international evidence-based practice guidelines [92]. Dietetic care for hemodialysis patients in Lebanon suffers from the absence of regulating policies, the lack of continuous education or certification programs in renal dietetics, the lack of integrating dietitians into the medical team, the unavailability of culturally-specific educational tools, and limited time for providing evidence-based practice nutritional care [94,95]. In parallel, Lebanese hemodialysis patients exhibit poor nutrition-related outcomes and might be at risk of malnutrition [91,96]. Specifically, hyperphosphatemia is a common finding. Despite the fact that 88% of patients use phosphate binders [91], around 41% of Lebanese hemodialysis patients are hyperphosphatemic [96].

The *Nutrition Education for Management of Osteodystrophy (NEMO)* [96] is a randomized controlled trial conducted in 12 hospital-based hemodialysis units. Its design is displayed in Figure 1. NEMO proposed a novel model of care for hyperphosphatemia management in Lebanon, where dietitians are provided with sufficient skills, tools and time to provide nutrition education for hemodialysis patients. In more detail, NEMO assessed the effect of a 2-hour per month stage-based nutritional education program provided by dedicated dietitians on serum phosphorus control. NEMO compared this model of care (Dedicated Dietitian: DD, where two key factors of the nutrition education are ensured: (1) dietitian education, and (2) recommended dietitian-to-patient time following international guidelines) with the existing practice (Existing Practice: EP) in Lebanon, lacking both dietitian education and dietitian-to-patient time factors, and to a proposed alternative (Trained Hospital Dietitian: THD), where dietitian education is ensured through an intensive training similar to one applied in the DD group, yet contact time with hemodialysis patients is not established. NEMO reported significantly improved serum phosphorus management, increased adherence to a low-phosphorus diet, increased knowledge related to the low-phosphorus diet, slower deterioration in some components of QOL and in the nutritional status of the general hemodialysis population [94,97]. However, the effect of this intervention specifically on patients with hyperphosphatemia (in terms of serum phosphorus and nutritional status outcomes) was not explored. Assessing the impact of the nutrition education among this sub-population is of utmost importance, since these patients exhibit unique demographic and clinical characteristics, are at increased morbimortality risk due to their elevated serum phosphorus level and for whom the intervention aiming to decrease serum phosphorus is appropriately targeted.

In addition to the positive clinical effect of this intervention, it would be important for decision makers to know its value for money spent. Accordingly, an economic evaluation should be performed.

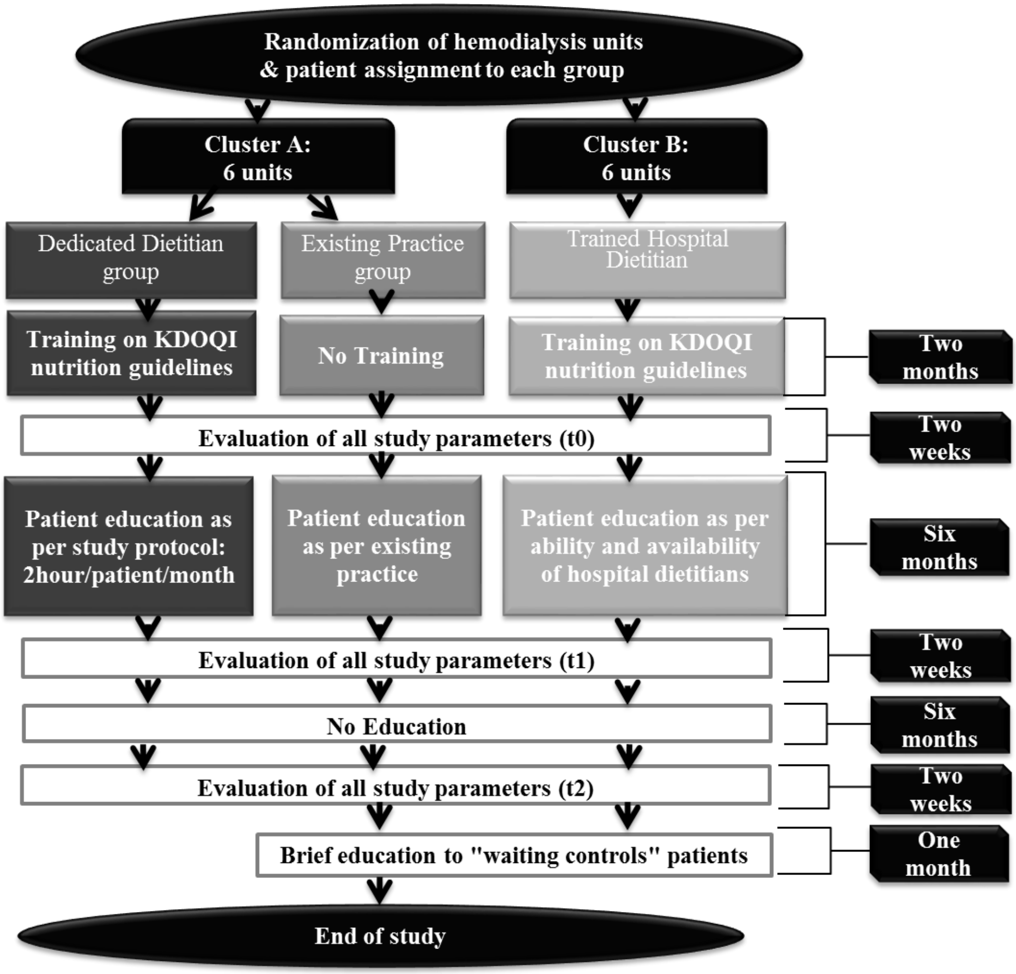

Figure 1. *Design of the NEMO Trial* [96].

HEALTH TECHNOLOGY ASSESSMENT AND ECONOMIC EVALUATIONS IN LEBANON

Over a decade ago, the promotion of the creation of a national HTA agency was suggested as a core component of the strategy for national health care reform in Lebanon [5]. This agency would be responsible for initiating a systematic approach for value-based care in the country and informing public health decision making, through research, collection of information, analysis and reporting on the cost-effectiveness of health technologies [5]. Yet, to date, no concrete steps in this regard have been undertaken, save for a few exceptions in oncology management and immunotherapy, where decisions have recently been taken with a focus on budget impact [6]. Implementing a national program for HTA was mainly deferred due to the shortage of local expertise and multi-disciplinary specialists in the public sector, the lack of epidemiological and clinical data, the absence of clearly defined health priorities and health outcomes needs, and improper communication and collaboration between stakeholders in health care [5,6]. Similarly, the performance and dissemination of economic evaluations in Lebanon is uncommon. For instance, a search conducted on February 20, 2017 of Pubmed employing the terms of ("Technology Assessment, Biomedical"[Mesh] OR "Cost-Benefit Analysis"[Mesh]) AND "Lebanon"[Mesh] results in only 11 records. Another search of the University of York's Centre for Reviews and Dissemination (CRD) on the NHS Economic Evaluation Database (NHS EED) and HTA database using the "Lebanon"[Mesh] results in only 1 record.

OBJECTIVES AND OUTLINE OF THE THESIS

The aim of this dissertation is to provide insights into the HTA of hyperphosphatemia management among hemodialysis patients in Lebanon and explore economic considerations in this regard.

The objectives are to provide an overview of the cost-effectiveness of interventions for hyperphosphatemia management among hemodialysis patients; to explore the financial burden of hemodialysis and hyperphosphatemia management in Lebanon and to evaluate the clinical and economic value of intensive nutrition education as a phosphorus-lowering intervention.

More specifically, in ***Chapter 2***, we systematically review and critically appraise the available evidence regarding the cost-effectiveness of interventions for managing hyperphosphatemia among hemodialysis patients. In fact, although an increasing number of economic evaluations of phosphorus-lowering interventions are being published, the evidence behind the comparative cost-effectiveness of these agents is still scarce, and their quality is understudied. In ***Chapter 3***, in light of the scarcity of economic information on hemodialysis in Lebanon, we provide detailed estimates on the societal cost-of-illness of this RRT and its main drivers, using data from the NEMO trial. We also gain insights into the financial burden of hyperphosphatemia management in this patient population in Lebanon. The remaining 2 chapters explore the clinical and economic value of a novel model of dietetic care for hyperphosphatemia management among hemodialysis patients in Lebanon. ***Chapter 4*** explores the impact of intensive nutrition education provided by dedicated dietitians on serum phosphorus management among hemodialysis patients with hyperphosphatemia and compares this intervention with existing practices in Lebanon and with a proposed alternative. Finally, ***Chapter 5*** explores the societal cost-effectiveness and cost-utility of this intervention, and informs decision makers about its value for money spent. The objectives of this dissertation are summarized in Figure 2.

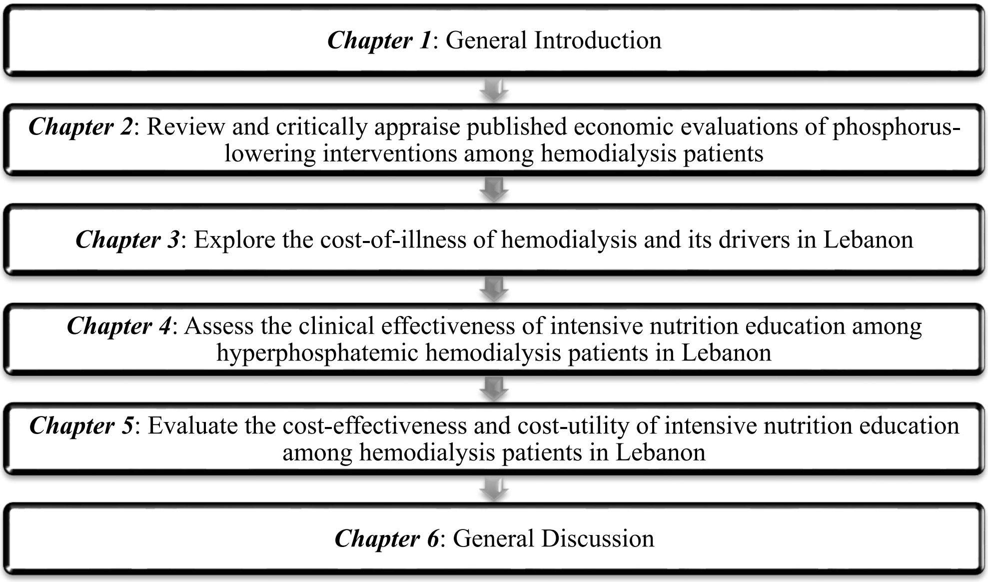

Figure 2. *Outline of the dissertation.*

Chapter 6 reviews the major findings of the dissertation and discusses its methodological challenges, strengths and limitations, as well as its clinical, economic, societal, public health and research implications.

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CHAPTER 2

ECONOMIC EVALUATIONS OF INTERVENTIONS TO MANAGE HYPERPHOSPHATAEMIA IN ADULT HAEMODIALYSIS PATIENTS: A SYSTEMATIC REVIEW

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ABSTRACT

Managing hyperphosphataemia in haemodialysis patients is resource-intensive. A search for cost-effective interventions in this field is needed to inform decisions on the allocation of healthcare resources. NHSEED, MEDLINE, EMBASE and CINAHL were searched for full economic evaluations of hyperphosphataemia-managing interventions in adult haemodialysis patients, published between 2004 and 2014, in English, French, Dutch or German. Incremental cost-effectiveness ratios of the interventions were up-rated to 2013US$ using Purchasing Power Parity conversion rates and Consumer Price Indices. The quality of included studies was assessed using the Extended Consensus on Health Economic Criteria List. Twelve out of the 1681 retrieved records fulfilled the inclusion criteria. They reported only on one aspect of hyperphosphataemia management, which is the use of phosphate binders (calcium-based and calcium-free, in first-line and sequential use). No economic evaluations of other phosphorus-lowering interventions were found. The included articles derived from five countries and most of them were funded by pharmaceutical companies. The incremental cost-effectiveness ratios of phosphate binders ranged between US$11,461 and US$157,760 per quality-adjusted life-year gained. Calcium-based binders (especially calcium acetate) appear to be the optimal cost-effective first- and second-line therapy in prevalent patients, while the calcium-free binder, lanthanum carbonate, might provide good value for money, as second-line therapy, in incident patients. The studies' overall quality was suboptimal. Drawing firm conclusions was not possible due to the quality heterogeneity and inconsistent results. Future high-quality economic evaluations are needed to confirm the findings of this review and to address other interventions to manage hyperphosphataemia in this population.

KEYWORDS

Cost-benefit analysis; hyperphosphatemia; kidney failure, chronic; renal dialysis.

INTRODUCTION

Renal failure is a growing public health problem [1], with haemodialysis (HD) being its primary treatment modality. Elevated serum phosphorus- hyperphosphataemia- is one particular complication of renal failure. It is consistently and independently associated with several adverse outcomes such as the chronic kidney disease- mineral bone disorder (CKD-MBD) and increased risk of morbidity and mortality [2,3]. Normalizing serum phosphorous is suggested as essential for achieving adequate mineral-bone metabolism and improving survival [4,5]. Serum phosphorus management relies on dietary restriction, removal from the blood through dialysis and the use of phosphate-binding medications to reduce intestinal absorption [4,5]. Currently used binders are calcium-based: calcium acetate (CA), calcium carbonate (CC)... or calcium-free: sevelamer, lanthanum carbonate (LC) [6]… Finally, novel iron-based agents may be soon available for the treatment of hyperphosphatemia [6].

Hyperphosphataemia and its management pose a high financial burden on the patients and healthcare systems [7,8], and given the scarcity of resources, integrating health-economic evaluations while formulating evidence-based practice guidelines is highly recommended [9]. Economic evaluations of healthcare interventions provide evidence for value of money spent [9] and are now increasingly used to assist policymakers in resource allocation [10].

Several reviews in this field were previously conducted [11-13]. Komaba et al. [11] and Goto et al. [12] suggested LC as a cost-effective second-line therapy, especially in patients with moderate to severe hyperphosphataemia. In these reviews, however, the cost-effectiveness of first-line sevelamer and that of LC versus (vs.) sevelamer were not established [11,12]. CA combined with magnesium carbonate was suggested by Plagemann et al. [13] as a cost-effective first-line therapy. However, this review [13] did not include any full economic evaluation of this combination and was funded by the pharmaceutical industry. None of these reviews adopted a systematic methodology nor critically appraised the quality of included studies. Moreover, they focused only on the cost-effectiveness of phosphate binders (PB). We could not identify any systematic review exploring the cost-effectiveness of different types of hyperphosphataemia-managing interventions in adults undergoing HD.

Therefore, we aim to systematically review the evidence on the economic evaluations of different phosphorus-lowering interventions, whether related to dialysis, pharmacotherapy or diet. We also aim to assess the quality of included studies and identify research gaps in this field in order to generate valid, reliable and transparent conclusions to policymakers and researchers.

METHODS

Standard methods for conducting and reporting systematic reviews (PRISMA) [14] were used. The protocol of this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42014014631).

LITERATURE SEARCH STRATEGY

A search for published economic evaluations was performed on NHSEED, MEDLINE, EMBASE and CINAHL. An exhaustive search strategy employing the most sensitive search filters [15,16] to retrieve economic evaluations was elaborated. For the other terms, HD and hyperphosphataemia, the search included free-text words and controlled vocabulary. The search strategy was validated by an information specialist and is available in Supporting Information Appendix S1. The references of eligible studies were searched to identify papers missed by database searches. Finally, searches were rerun before the final analyses (01-01-2015).

INCLUSION AND EXCLUSION CRITERIA

Preset inclusion criteria consisted of: original article; intervention for hyperphosphataemia management in adults undergoing maintenance HD; full economic evaluation comparing the costs and consequences of two or more interventions [17], namely cost-benefit, effectiveness and utility analyses; article in English, French, Dutch or German; and published between 01-01-2004 (after the release of K/DOQI Guidelines for Bone Metabolism and Disease [5]) and 31-12-2014.

SELECTION OF STUDIES

Two reviewers screened retrieved titles and abstracts to identify potentially eligible studies. At least two reviewers independently assessed the full texts of these studies against inclusion criteria. Disagreements were resolved by discussion.

DATA EXTRACTION, DATA ANALYSIS AND QUALITY ASSESSMENT

At least two reviewers independently performed evidence synthesis and critical appraisal, using standardized forms. Disagreements were resolved by discussion or with a third author, where necessary. A descriptive synthesis of the characteristics of the included studies was done. The primary source of effectiveness used for conducting the analysis, the population, the comparator and the results of the base-case analysis (incremental cost-effectiveness ratios (ICER) reported as cost per life-year (LY) or quality-adjusted life-year (QALY) gained) were reported. Results of subgroup and sensitivity analyses were reported, when available. To enable comparability across studies, all incremental ratios were converted to US$, using Purchasing Power Parity (PPP) conversion rates [18], and up-rated to 2013US$ using Consumer Price Indices (Index, 2010=100) [19]. A cost-effectiveness threshold of US$50,000/QALY was applied [20]. For quality assessment, reviewers used the Extended Consensus on Health Economic Criteria (CHEC) List [21], in which the CHEC List [22] was extended with one question on modelling assumptions and validation. Twenty items were scored using: Yes (1), Suboptimal (0.5), No (0) and Not Applicable. The maximum score was 19 for trial-based economic evaluations and 20 for models.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS, version 21. Independent-samples t-test and Fisher's exact test were employed to investigate the associations between the studies' characteristics and quality. Statistical significance was accepted at $P<0.05$.

RESULTS

The search retrieved 1681 records of which 12 articles were included in the analysis (Figure 1).

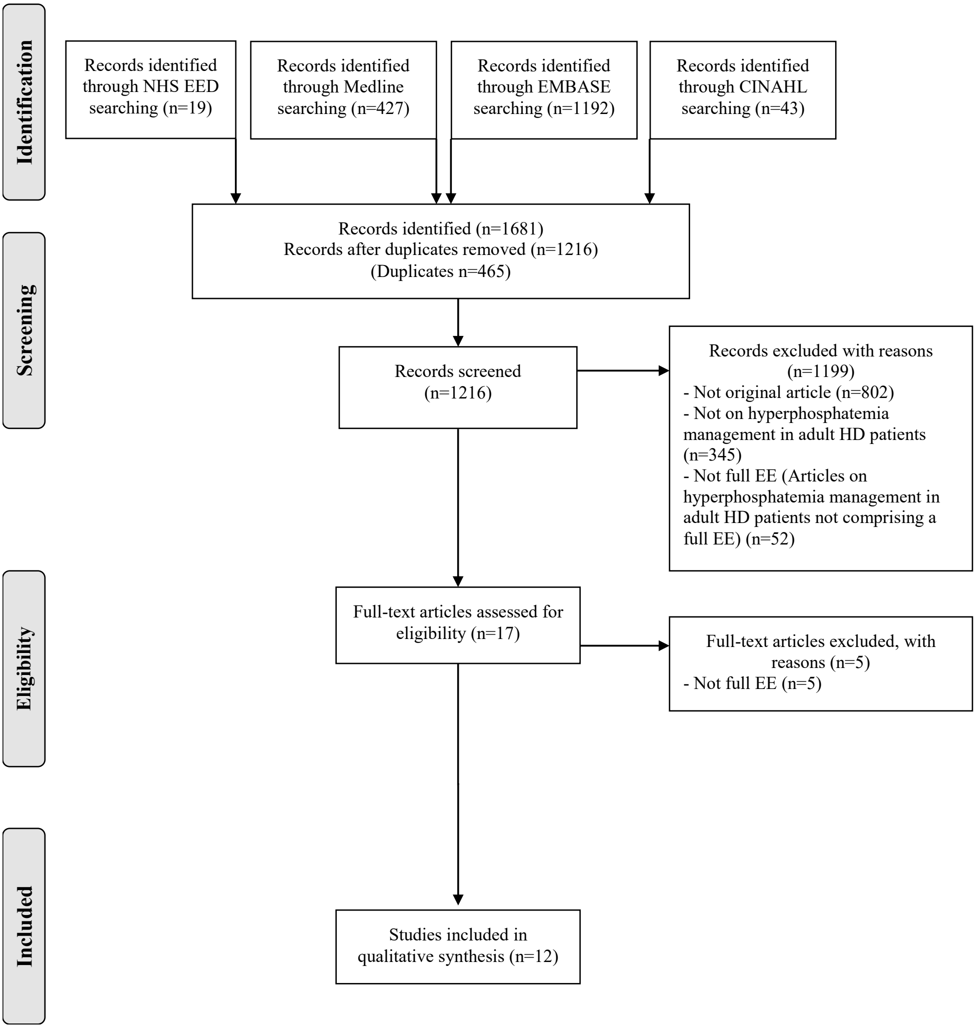

Figure 1. *Flow chart of the inclusion process of search results.*
EE, economic evaluation; HD, haemodialysis. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med.* 2009; 6: e1000097. doi: 10.1371journal.pmed1000097.

OVERVIEW OF INCLUDED STUDIES

All included articles reported on the cost-effectiveness of only one type of intervention, which is the use of PB. As reported in Table 1, included studies were mostly conducted in the United Kingdom (n=5) [23,26,28,41,43]. Half of the articles were published in pharmacoeconomic journals [23,26,32,34,37,43] and eight studies were funded by pharmaceutical companies [23,26,32,34,37,41,43,44]. All articles adopted a payer perspective and all except Ruggeri et al. [39] used model-based analysis, especially markov models (n=6) [23,35,37,41,43,44]. QALY were outcome measures in four studies [26,28,31,35], and QALY and LY in five studies [23,37,41,43,44]. Incident [39,41,43,44] and prevalent [23,26,28,31,32,34,37] patients were studied; with the majority being hyperphosphataemic. The studied binders were calcium-based, mainly CC and CA and calcium-free, mainly sevelamer hydrochloride (SH) and LC. Five studies [26,28,31,43,44] compared the cost-effectiveness of PB as second-line therapy. Details on populations, comparators, results and sensitivity analyses are found in Supporting Information Appendix S2.

RESULTS OF INCLUDED STUDIES

Figures 2, 3 and 4 present the comparators and main results of the articles. When compared with calcium-based binders, CBB: CC and/or CA, the cost-effectiveness of calcium-free binders in prevalent patients was inconsistent between studies. The most studied one was sevelamer [23,28,32,34,35,37,39,41]. Its ICER ranged from greatly above US$100,000 [28,35] to US$36,803/QALY gained [23]. First-line calcium-free binders in prevalent patients were compared only in Park et al. [37], where LC had an ICER of US$26,835/QALY gained. SH was the only studied calcium-free binder vs. CBB in incident patients, with an ICER of US$47,153/QALY gained [45]. For first-line use, CA appear to be the most cost-effective therapy with an ICER of US$11,818/QALY gained [28]. The results of the cost-effectiveness of second-line PB in prevalent patients derived mainly from Dasgupta et al. [28] (we reviewed the methods and results of this study, which are available in the Appendix F of the NICE clinical guideline 15735). The continuous use of CA was the most cost-effective intervention with an ICER of US$11,818/QALY gained. Switching from CA to SH was slightly above the cost-effectiveness threshold, leading to an ICER of (US$54,898/QALY gained, compared with CC. All other treatment strategies were dominated (less effective and more costly) or extendedly dominated (producing additional gains in effectiveness at incremental costs higher than those of the next most effective strategy). Brennan et al. [26] reported that LC was cost-effective when compared with CC (US$48,787/QALY gained). The ICER of LC further decreased when compared with a treatment including SH and CBB and reached US$33,396/QALY gained [31]. In incident patients, second-line LC vs. CBB offered good value for money [43,44], with ICERs ranging between US$11,461 and US$11,525/QALY gained.

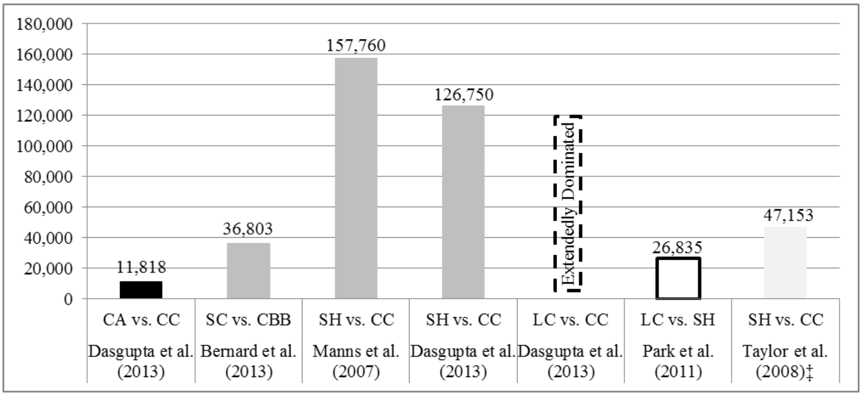

Figure 2. *Incremental cost-effectiveness ratios of phosphate binders in first-line use.* Incremental cost-effectiveness ratios (ICER) are up-rated to 2013US$; ICER are reported as US$/quality-adjusted life-years (QALY) gained. Different colours represent different set of comparators. ‡Incident patients. CA, calcium acetate; CBB, calcium-based binders; CC, calcium carbonate; LC, lanthanum carbonate; SC, sevelamer carbonate; SH, selevamer hydrochloride.

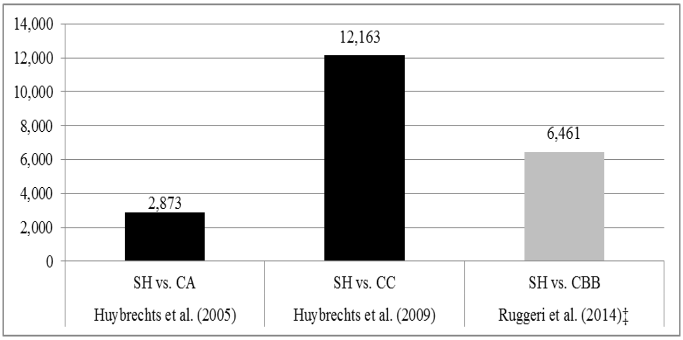

Figure 3. *Incremental cost-effectiveness ratios of phosphate binders in first-line use.* Incremental cost-effectiveness ratios (ICER) are up-rated to 2013US$; ICER are reported as US$/life-years (LY) gained. Different colours represent different set of comparators. ‡Incident patients. CA, calcium acetate; CBB, calcium-based binders; CC, calcium carbonate; SH, selevamer hydrochloride.

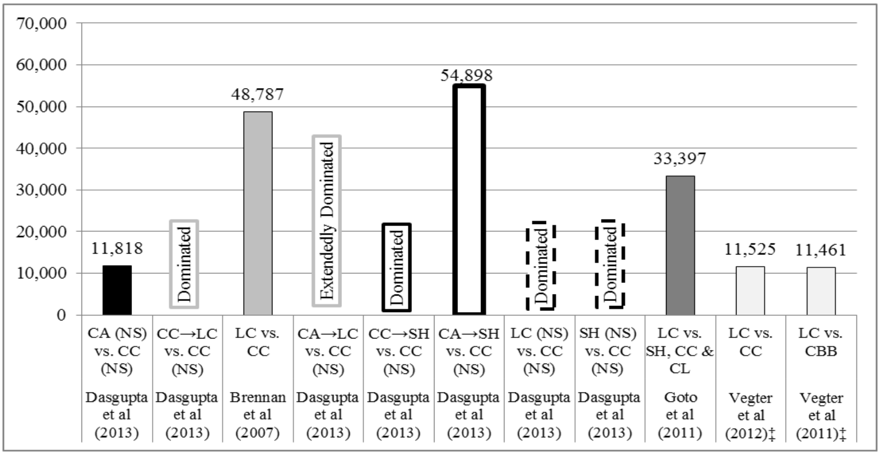

Figure 4. *Incremental cost-effectiveness ratios of phosphate binders in second-line use.* Incremental cost-effectiveness ratios (ICER) are up-rated to 2013US$; ICER are reported as US$/ quality-adjusted life-years (QALY) gained. Different colours represent different set of comparators. ‡Incident patients. CA, calcium acetate; CBB, calcium-based binder; CC, calcium carbonate; CL, calcium lactate; LC, lanthanum carbonate; NS, no switch; SH, selevamer hydrochloride.

Table 1. *Characteristics of included studies*

Authors & Year	Journal	Country	Study Design/ Model type	Type of EE	Primary Source of Effectiveness	Outcome Measure	Cost Perspective	Time Horizon	Currency (year) & Discount Rates/year	Funding
Bernard, 2013 [23]	Journal of Medical Economics	UK	Markov health-state transition model	CEA CUA	DCOR study (Suki et al., 2007 [24], 2008 [25])	LY QALY	Health care payer (NHS)	Lifetime	Currency: British Pounds (£) (2009) Discounting: 3.5%	Genzyme Corporation
Brennan, 2007 [26]	Value in Health	UK	Model of clinical pathways	CUA	Hutchison et al., 2005 [27]	QALY	Health care payer (NHS)	Lifetime	Currency: British Pounds (£) (NR) Discounting: 3.5%	Pharmaceuticals Group plc.
Dasgupta, 2013 [28] (NICE Clinical Guideline 157: Appendix F) [29]	Nephron Clinical Practice (Full report: NICE Clinical Guideline 157)	UK	Discrete event individual patient simulation model	CUA	Braun et al., 2004 [30]	QALY	Health care payer (NHS and (Personal Social Services))	Lifetime	Currency: British Pounds (£) (fracture, parathyroidectomy, transplantation, blood tests, dialysis: 2011, drugs: 2012) Discounting: 3.5%	NICE
Goto, 2011 [31]	Clinical Journal of the American Society of Nephrology	Japan	Patient-level state transition model	CUA	Goto et al., 2011 [31]	QALY	Health care system	Lifetime	Currency: Japanese Yen and converted to US dollars ($1= ¥100) (2010) Discounting: 3%	NR
Huybrechts, 2005 [32]	Value in Health	USA	Discrete event individual patient simulation model	CEA	TTG study (Chertow et al., 2002 [33])	LY CV event prevented	Payer providing full health care coverage	Lifetime (13 years)	Currency: US dollar ($)(2002) Discounting: 3% for cost and benefits beyond 1 year	Genzyme Corporation
Huybrechts, 2009 [34]	Value in Health	Canada	Discrete event simulation	CEA (adapted from Huybrechts et al., 2005 [32])	TTG study (Chertow et al., 2002 [33])	LY	Canadian Medicare	Lifetime (13 years)	Currency: Canadian dollar ($) (2005) Discounting: 3%	Genzyme Canada
Manns, 2007 [35]	Nephrology Dialysis Transplantation	Canada, USA	Markov model	CUA	DCOR study (Suki et al., 2005 [36])	QALY	Health care purchaser (publicly funded government health care in Canada and Medicare in the USA)	Lifetime	Currency: Canadian dollar (1US$ = 1.30CAN$) and US dollar ($) for the USA scenario analyses (2004) Discounting: 5%	CADTH

Authors & Year	Journal	Country	Study Design/ Model type	Type of EE	Primary Source of Effectiveness	Outcome Measure	Cost Perspective	Time Horizon	Currency (year) & Discount Rates/year	Funding
Park, 2011 [37]	Value in Health	USA	Markov model	CEA CUA	Sprague et al., 2009 [38]	LY QALY	Health care payer	10 years	Currency: US dollar ($)(2009) Discounting: 5%	Shire Pharmaceuticals
Ruggeri, 2014 [39]	Journal of Nephrology	Italy	Trial-based EE	CEA	INDEPENDENT study (Di Iorio et al., 2013 [40])	LY	NHS (Servizio Sanitario Nazionale)	3 years	Currency: Euro (€) (2012) Discounting: None	The Italian National Health Care System funded the INDEPENDENT study. No funding was provided for the conduct of the EE study. Funding was provided by Sanofi to Cornerstone Research Group to write the manuscript on behalf of the authors
Taylor, 2008 [41]	Current Medical Research and Opinion	UK	Markov health state transitions model	CEA CUA	RIND study (Block et al., 2007 [42])	LY QALY	Health care payer (NHS)	5 years	Currency: British Pounds (£)(2007) Discounting: 3.5%	Genzyme Therapeutics
Vegter, 2011 [43]	Value in Health	UK	Time-dependent, life-long Markov model	CEA CUA	Hutchison et al., 2005 [27]	LY QALY	Health care payer (NHS)	Lifetime (max 40 years)	Currency: British Pounds (£)(2009) Discounting: 3.5%	Shire Pharmaceuticals
Vegter, 2012 [44]	Clinical Therapeutics	Canada	Time-dependent Markov model	CEA CUA (adapted from Vegter et al., 2011 [43])	Hutchison et al., 2005 [27]	LY QALY	Health Care Payer	Lifetime	Currency: Canadian dollar (CAN$) (2010) Discounting: 5%	Shire Pharmaceuticals

EE: Economic Evaluation; UK: United Kingdom; CEA: cost-effectiveness analysis; CUA: cost-utility analysis; DCOR: Dialysis Clinical Outcomes Revisited; LY: life-year; QALY: quality-adjusted life-year; NHS: National Health Service; NR: not reported; NICE: National Institute for Health and Care Excellence ; USA: United States of America; TTG: Treat-To-Goal ; CV: cardiovascular; CADTH: Canadian Agency for Drugs and Technologies in Health; RIND: Renagel In New Dialysis

In subgroup analyses, the ICER of first-line calcium-free binders slightly decreased when older patients (≥65 years) were included in Bernard et al. [46]; the opposite was found by Manns et al. [35], Taylor et al. [41] and Dasgupta et al. [28]. The sequential use of calcium-free binders in severely hyperphosphataemic patients resulted in better cost-effectiveness [26], where the ICER of LC vs. CC dropped from US$241,334/QALY gained in patients with serum phosphorus of 5.6-6.5 mg/dL to US$17,413/QALY gained in patients with serum phosphorus above 7.9 mg/dL.

In sensitivity analyses, results were robust to changes in various model parameters in the majority of the studies. The most common influential factors were efficacy, drug costs, time horizon (i.e. shorter horizons resulted in higher ICERs; especially for calcium-free binders in sequential use), utility of renal failure and inclusion of future unrelated costs. In fact, whenever included, dialysis costs resulted in much higher ICERs. Finally, studies funded by pharmaceutical companies were more likely to report ICERs favouring their sponsors (P=0.018).

RESULTS OF THE QUALITY ASSESSMENT

Quality assessment results are displayed in Table 2. The only included trial-based economic evaluation [39] scored 10/19. Mean quality scores for models was 14.77±2.19 (11.50-19.00). The economic study design was appropriate in all articles. However, description of the study population [23,26,35,37,41,43,44] and conduct of deterministic and probabilistic sensitivity analyses [23,26,28,31,35,39,41,43] were suboptimal in more than half of the studies. Reporting structural assumption and validation of the model was suboptimal in seven studies [23,26,32,34,41,43,44]. Costs and outcomes were not appropriately discounted in four studies [31,34,37,39]. Studies that were not funded by pharmaceutical companies [28,35] had significantly higher scores (18.00 vs. 13.55; P=0.01). The majority of high-quality studies favoured first- and second-line use of CBB over calcium-free binders in prevalent patients [28,35]. Only one high-quality study [44], funded by the industry, reported better cost-effectiveness of second-line LC over CBB, in incident patients.

Table 2. *Quality assessment scores*

	Bernard 2013 [23]	Brennan 2007 [26]	Dasgupta 2013 [38]	Goto 2011 [31]	Huybrechts 2005 [32]	Huybrechts 2009 [34]	Manns 2007 [35]	Park 2011 [37]	Ruggeri 2014 [39]	Taylor 2008 [41]	Vegter 2011 [43]	Vegter 2012 [44]
1- Is the study population clearly described?	0.5	0.5	1	1	1	1	0: no clear description	0.5	1	0.5	0.5	0.5
2- Are competing alternatives clearly described?	0.5	1	1	1	0: no clear description	0: no clear description	0.5	1	0.5	1	1	1
3- Is a well-defined research question posed in answerable form?	1	1	1	1	0: not clearly defined	0: not clearly defined	0.5	1	1	1	1	1
4- Is the economic study design appropriate to the stated objective?	1	1	1	1	1	1	1	1	1	1	1	1
5- Are the structural assumptions and the validation methods of the model properly reported? (only for models)	0.5	0.5	1	1	0.5	0.5	1	1	NA	0.5	0.5	0.5
6- Is the chosen time horizon appropriate in order to include relevant costs and consequences?	1	1	1	1	1	1	1	1	0.5	0.5	1	1
7- Is the actual perspective chosen appropriate?	1	1	1	1	1	1	1	1	0.5	1	1	1
8- Are all important and relevant costs for each alternative identified?	1	0.5	1	0.5	1	1	1	1	0.5	1	0.5	1
9- Are all costs measured appropriately in physical units?	0.5	0.5	1	1	1	1	1	0.5	0: no valid source	0.5	1	1
10- Are costs valued appropriately?	1	0.5	1	0: PPP not used to convert to US$	1	1	1	1	0.5	0.5	0.5	0.5
11- Are all important and relevant outcomes for each alternative identified?	1	1	1	0.5	0.5	0.5	1	1	0.5	1	1	1

	Bernard 2013 [23]	Brennan 2007 [26]	Dasgupta 2013 [38]	Goto 2011 [31]	Huybrechts 2005 [32]	Huybrechts 2009 [34]	Manns 2007 [35]	Park 2011 [37]	Ruggeri 2014 [39]	Taylor 2008 [41]	Vegter 2011 [43]	Vegter 2012 [44]
12- Are all outcomes measured appropriately?	1	1	1	1	0: modular algorithms not completely disclosed	0: modular algorithms not completely disclosed	1	1	0.5	1	1	1
13- Are outcomes valued appropriately?	1	1	1	1	0: modular algorithms not completely disclosed	0: modular algorithms not completely disclosed	1	1	1	0.5	1	1
14- Is an appropriate incremental analysis of costs and outcomes of alternatives performed?	1	1	1	1	1	1	1	1	1	0.5	1	1
15- Are all future costs and outcomes discounted appropriately?	1	1	1	0.5	1	0.5	1	0.5	0: no discounting applied	1	1	1
16- Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	0: important parameters not all included; no PSA	0.5	0.5	0.5	1	1	0.5	1	0.5	0: important parameter s not all included; no PSA	0.5	1
17- Do the conclusions follow from the data reported?	1	1	1	1	1	1	1	1	0.5	0.5	1	1
18- Does the study discuss the generalizability of the results to other settings and patient/client groups?	0.5	0: no discussion	1	1	0: no discussion	0: no discussion	1	0: no discussion	0: no discussion	0: no discussion	0: no discussion	0: no discussion
19- Does the article/ report indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	0: conflict of interest disclosed	0: conflict of interest disclosed	1	0: conflict of interest disclos ed	0: conflict of interest disclosed	0: conflict of interest disclosed	1	0: conflict of interest disclosed	0: conflict of interest disclosed	0: conflict of interest disclosed	0: conflict of interest disclosed	0: conflict of interest disclosed
20- Are ethical and distributional issues discussed appropriately?	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0: no discussion	0.5	0: no discussion	0: no discussion	0: no discussion
CHEC list score	15	14.5	19	15.5	12.5	12	17	15.5	10	12	14.5	15.5

NA: not applicable; PPP: purchasing power parity; PSA: probabilistic sensitivity analysis

DISCUSSION

Our results confirm what was suggested by Komaba et al. [11] and Goto et al. [12] on the lack of conclusive evidence advocating the systematic use of sevelamer in real clinical settings. While both reviews suggested LC as a cost-effective sequential therapy, our results support this use only in incident patients. The use of calcium-free binders in HD patients was promoted because of their association with lower rates of treatment-related hypercalcaemia, which may reduce vascular calcification [33,47]. However, recent high-quality evidence did not establish their superiority over CBB in terms of serum phosphorus management [46]. Regarding HD patient mortality, two recent meta-analyses studied the impact of calcium-free binders vs. CBB and reported inconsistent results [46,48]. Plagemann et al. [13] proposed the novel preparation of CA and magnesium carbonate as a cost-effective first-line therapy; our extensive search did not result in any economic evaluation of this combination.

The included studies differed in several areas, such as patient populations: prevalent vs. incident, study design: markov model, patient-level simulation, trial-based..., primary source of efficacy: phosphorus control vs. survival, costs included: dialysis, transplantation... and their sources, health utilities... and were conducted in five different countries. All these factors affect the validity of the direct comparison of the findings of these studies [49] and hinder our ability to make clear recommendations on the relative cost-effectiveness of PB. This was also indicated in systematic reviews in other areas of healthcare [45]. For these reasons, and taking into consideration the descriptive nature of this review, the validity of the results of the included studies and subsequently this review should be interpreted with caution.

Our secondary aim was to assess the quality of included articles. On average, scores were suboptimal and this was mainly due to the numerous methodological shortcomings and poorly justified modelling assumptions. Suboptimal quality of economic evaluations was also reported by previous systematic reviews [45,50,51].

STRENGTHS AND LIMITATIONS OF THIS SYSTEMATIC REVIEW

Although this systematic review provides valuable information for researchers and policymakers, the overall evidence behind its findings was suboptimal. While previous reviews focused on the cost-effectiveness of PB only, this review pioneered in systematically searching for economic evaluations of all phosphorus-lowering interventions. We followed standard methods for conducting and reporting systematic reviews and exhaustively searched multiple databases. However, we did not search the grey literature and were limited to articles published after the release of K/DOQI guidelines [5], the first guidelines to assist decision-making in the field of hyperphosphataemia management in HD patients.

We followed recommended steps [52] for converting ICERs to the same currency for the same year, to enable comparison between the studies and generate potentially applicable conclusions to different countries. Another limitation of this review is the adopted cost-effectiveness threshold of US$50,000- a conveniently cited value in the USA [20]. Cost-effectiveness thresholds are influenced by healthcare resources, reimbursement mechanisms, cultural and social factors, and thus differ between countries [53]; however, due to the heterogeneity in results, changing the threshold would not have affected our conclusion.

We also appraised the quality of included studies; a first in the field of economic evaluations of PB. Despite using a validated checklist, differences in quality judgment might be due to the contribution of all reviewers in this process. The mean quality of included studies was suboptimal in nature and most of them were funded by pharmaceutical companies. Lexchin et al. [54] reported that pharmacoeconomic studies sponsored by the industry tended to favour the sponsor's product; we found similar results. Finally, for some comparators or situations, only one study/model was found. All these factors affect the quality of our findings and limit our ability to draw firm conclusions.

IMPLICATIONS FOR RESEARCHERS

Several research gaps were identified. We did not find any publication on the cost-effectiveness of other interventions for hyperphosphatemia management despite their increasing use in clinical practice, such as dietary interventions, exercise during dialysis and non-dialysis times, dialysis prescription (long vs. standard hour and frequent vs. standard dialysis), and adherence-promoting interventions. Economic evaluations of these interventions are needed, especially in the fields of dialysis prescription and adherence promotion, as they were effective in terms of decreased serum phosphorus [55-57] and phosphate binders dose [57], an resulted sin better survival [56], improved quality-of-life [58], and cost savings [59], among others. Several drawbacks were mentioned in the included articles, primarily pertaining to the lack of data in the following areas: long-term effects of PB on survival and other health outcomes; cost impact and utility of hypercalcaemic events; utility of different PB and their side effects, adherence rates with different binders and their effects on outcomes and costs… Also, we could not identify any head-to-head comparison between calcium-free binders. Goto et al. [31] assessed second-line LC vs. a treatment comprising SH, CC and calcium lactate, and found that the former was cost-effective. In contrast, Vegter et al. [44] performed a cost-minimization analysis between second-line LC and SH, and reported that the former was 23% less expensive; full economic evaluations of these agents are needed. Economic evaluations between LC and sevelamer are also needed in patients with hypercalcaemia and who do not tolerate CBB. Finally, further research is needed to better understand the cost-effectiveness of PB in certain populations, especially elderly, severely hyperphosphataemic, hypercalcaemic...

IMPLICATIONS FOR PUBLIC-HEALTH POLICYMAKERS

Although hyperphosphataemia and its management pose clinical and financial burdens in HD patients worldwide, included articles derived from five high-income countries only. This highlights the lack of country-specific economic evaluations, particularly in low- and middle-income countries. Until further country-specific research is available, the results of this systematic review might be used by decision makers who are constantly faced by healthcare resource constraints. More evidence is needed to inform policy-makers whether the cost of high-cost binders is warranted, especially that up-till-now, no controlled randomized trial had supported the benefits of lowering serum phosphorus to suggested targets, on patient-level end points [4,5].

CONCLUSION

In conclusion, we found limited high-quality evidence on the cost-effectiveness of PB in adult HD patients. Their ICER ranged between US$11,461 and US$157,760/QALY gained. In view of the quality heterogeneity and inconsistent results of included studies, it was not possible to draw firm conclusions. CBB- especially CA, appear to be the most cost-effective therapy, in first-line and sequential use, in prevalent patients. LC might provide good value for money, as second-line therapy, in incident patients. We were not able to identify any study on other interventions to manage hyperphosphataemia in this population. Future high-quality economic evaluations are needed.

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Supporting Information Appendix S1: Search strategy

1) NHSEED via CRD

((MeSH DESCRIPTOR Phosphorus EXPLODE ALL TREES) OR (MeSH DESCRIPTOR Phosphates EXPLODE ALL TREES) OR (phosphorus or phosphat* or hyperphosphat* or hyper-phosphat*)) AND ((MeSH DESCRIPTOR Kidney Failure, Chronic EXPLODE ALL TREES) OR (MeSH DESCRIPTOR Renal Dialysis EXPLODE ALL TREES) OR (MeSH DESCRIPTOR Renal Insufficiency) OR (MeSH DESCRIPTOR Renal Replacement Therapy) OR (MeSH DESCRIPTOR Kidney Diseases OR MeSH DESCRIPTOR Uremia) OR (((renal OR kidney) NEAR3 (replacement* OR insufficien* OR impaire* OR failure OR disease*)) OR (dialys* OR hemodialys* OR haemodialys*) OR ((endstage* OR end-stage*) NEAR3 (renal OR kidney)) OR (uremi* OR azotemi* OR uraemi*) OR (chronic NEAR3 (renal OR kidney) NEAR3 injur*) OR (ESKD OR ESKF OR ESRD OR ESRF OR HD OR MHD))) IN NHSEED FROM 2004 TO 2014

2) MEDLINE using OVID

1. exp Economics/
2. quality of life/
3. value of life/
4. Quality-adjusted life years/
5. models, economic/
6. markov chains/
7. monte carlo method/
8. decision tree/
9. ec.fs.
10. economic$.tw.
11. (cost? or costing? or costly or costed).tw.
12. (price? or pricing?).tw.
13. (pharmacoeconomic? or (pharmaco adj economic?)).tw.
14. budget$.tw.
15. expenditure$.tw.
16. (value adj1 (money or monetary)).tw.
17. (fee or fees).tw.
18. "quality of life".tw.
19. qol$.tw.
20. hrqol$.tw.
21. "Quality adjusted life year$".tw.
22. qaly$.tw.
23. cba.tw.
24. cea.tw.
25. cua.tw.
26. utilit$.tw.
27. markov$.tw.
28. monte carlo.tw.
29. (decision adj2 (tree$ or analys$ or model$)).tw.
30. ((clinical or critical or patient) adj (path? or pathway?)).tw.
31. (managed adj2 (care or network?)).tw.
32. or/1-31
33. Letter.pt.

34. Editorial.pt.
35. Historical article.pt.
36. Animals/ not humans/
37. OR/33-36
38. 32 not 37
39. exp Hyperphosphatemia/
40. exp Phosphorus/
41. *Phosphates/
42. (phosphorus or phosphat* or hyperphosphat* or hyper-phosphat*).ti,ab,sh.
43. OR/39-42
44. exp Kidney Failure, Chronic/
45. exp Renal Dialysis/
46. exp Renal Insufficiency, Chronic/
47. Renal Replacement Therapy/
48. Renal Insufficiency/
49. *Kidney Diseases/
50. *Uremia/
51. ((renal or kidney) adj3 (replacement* or insufficien* or impaire* or failure or disease*)).ti,ab,sh.
52. (dialys* or hemodialys* or haemodialys*).ti,ab,sh.
53. ((endstage* or end-stage*) adj3 (renal or kidney)).ti,ab,sh.
54. (uremi* or azotemi* or uraemi*).ti,ab,sh.
55. (chronic adj3 (renal or kidney) adj3 injur*).ti,ab,sh.
56. (ESKD or ESKF or ESRD or ESRF or HD or MHD).ti,ab.
57. OR/44-56
58. 38 AND 43 AND 57
59. limit 58 to (yr="2004 -Current" and (dutch or english or french or german))

3) EMBASE using OVID

1. exp health economics/
2. exp health care cost/
3. exp quality of life/
4. economic$.tw.
5. (cost? or costing? or costly or costed).tw.
6. (price? or pricing?).tw.
7. (pharmacoeconomic? or (pharmaco adj economic?)).tw.
8. budget$.tw.
9. expenditure$.tw.
10. (value adj1 (money or monetary)).tw.
11. (fee or fees).tw.
12. "quality of life".tw.
13. qol$.tw.
14. hrqol$.tw.
15. "quality adjusted life year$".tw.
16. qaly$.tw.
17. cba.tw.
18. cea.tw.
19. cua.tw.
20. utilit$.tw.
21. markov$.tw.

22. monte carlo.tw.
23. (decision adj2 (tree$ or analys$ or model$)).tw.
24. ((clinical or critical or patient) adj (path? or pathway?)).tw.
25. (managed adj2 (care or network?)).tw.
26. OR/1-25
27. exp Hyperphosphatemia/
28. exp Phosphorus/
29. *Phosphate/
30. (phosphorus or phosphat* or hyperphosphat* or hyper-phosphat*).ti,ab,sh.
31. OR/27-30
32. exp Chronic Kidney Failure/
33. exp Hemodialysis/
34. exp Kidney Failure/
35. Renal Replacement Therapy/
36. *Kidney Disease/
37. *Uremia/
38. ((renal or kidney) adj3 (replacement* or insufficien* or impaire* or failure or disease*)).ti,ab,sh.
39. (dialys* or hemodialys* or haemodialys*).ti,ab,sh.
40. ((endstage* or end-stage*) adj3 (renal or kidney)).ti,ab,sh.
41. (uremi* or azotemi* or uraemi*).ti,ab,sh.
42. (chronic adj3 (renal or kidney) adj3 injur*).ti,ab,sh.
43. (ESKD or ESKF or ESRD or ESRF or HD or MHD).ti,ab.
44. OR/32-43
45. 26 AND 31 AND 44
46. Limit 46 to ((dutch or english or french or german) and yr="2004 -Current")

4) CINAHL using EBSCO

S1. MH "Economics+"
S2. MH "Financial Management+"
S3. MH "Financial Support+"
S4. MH "Financing, Organized+"
S5. MH "Business+"
S6. S2 OR S3 OR S4 OR S5
S7. S1 NOT S6
S8. MH "Health Resource Allocation"
S9. MH "Health Resource Utilization"
S10. S8 OR S9
S11. S7 OR S10
S12. TI (cost or costs or economic* or pharmacoeconomic* or price* or pricing*) OR AB (cost or costs or economic* or pharmacoeconomic* or price* or pricing*)
S13. S11 OR S12
S14. PT editorial
S15. PT letter
S16. PT commentary
S17. S14 or S15 or S16
S18. S13 NOT S17
S19. MH "Animal Studies"
S20. (ZT "doctoral dissertation") or (ZT "masters thesis")
S21. S18 NOT (S19 OR S20)

S22. MH "Hyperphosphatemia"
S23. MH "Phosphorus"
S24. MM "Phosphates"
S25. TI (phosphorus or phosphat* or hyperphosphat* or hyper-phosphat*) OR AB (phosphorus or phosphat* or hyperphosphat* or hyper-phosphat*)
S26. S22 OR S23 OR S24 OR S25
S27. MH "Kidney Failure, Chronic+"
S28. MH "Hemodialysis+"
S29. MH "Renal Insufficiency, Chronic+"
S30. MH "Renal Insufficiency"
S31. MM "Kidney Diseases"
S32. MM "Uremia"
S33. TI ((renal or kidney) N3 (replacement* or insufficien* or impaire* or failure or disease*)) OR AB ((renal or kidney) N3 (replacement* or insufficien* or impaire* or failure or disease*))
S34. TI (dialys* or hemodialys* or haemodialys*) OR AB (dialys* or hemodialys* or haemodialys*)
S35. TI ((endstage* or end-stage*) N3 (renal or kidney)) OR AB ((endstage* or end-stage*) N3 (renal or kidney)) 10. TI (uremi* or azotemi* or uraemi*) OR AB (uremi* or azotemi* or uraemi*)
S36. TI (chronic N3 (renal or kidney) N3 injur*) OR AB (chronic N3 (renal or kidney) N3 injur*)
S37. TI (ESKD or ESKF or ESRD or ESRF or HD or MHD) OR AB (ESKD or ESKF or ESRD or ESRF or HD or MHD)
S38 S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37
S39 S21 AND S26 AND S38
Limiters - Published Date: 20040101-20141231

Supporting Information Appendix S2: Results of included studies

Authors & Year	Population	Comparator	Main Results (ICER)	Adjusted ICER in $ for 2013 (Index, 2010=100)	Sensitivity Analysis
Bernard, 2013 [23]	Prevalent patients	S carbonate vs. CBB, as first line therapy (CA: 70% of patients; CC: 30% of patients)	For S carbonate vs. CBB: ICER: £22,157/QALY gained and £13,427/LY gained ICER in Sub-group analysis: ≥45 years: £15,864/QALY gained ≥55 years: £15,769/QALY gained ≥65 years: £13,296/QALY gained	For S carbonate vs. CBB: ICER: $36,803.29/QALY gained and $22,302.56/LY gained ICER in Sub-group analysis: ≥45 years: $26,350.48/QALY gained ≥55 years: $26,192.68/QALY gained ≥65 years: $22,084.97/QALY gained	One-way sensitivity analysis: Results were sensitive to: inclusion of annual cost of dialysis, overall survival for S carbonate vs. CBB; time horizon limited to 10 years and risk reduction in hospitalization days for the S carbonate group Probabilistic sensitivity analysis: NR
Brennan, 2007 [26]	Prevalent hyperphosphatemic patients	LC vs. CC, as second-line therapy: Policy 1: Continued CC Policy 2: LC trial (8 weeks), if successful continue LC, if unsuccessful switch to CC (+ Initially successful patients on LC but who become unsuccessful after long-term use of LC are switched back to CC)	For Policy 1 vs. Policy 2: CER: £14,906; 60,771; 26,847; 18,434/LY gained for lifetime, 2, 5 and 10 years respectively ICER: £25,033; 105,521; 45,389; 31,015/QALY gained for lifetime, 2, 5 and 10 years respectively ICER in Subanalysis (lifetime horizon): P>7.9 mg/dl: £8,935/QALY gained P: 6.6-7.8 mg/dl: £15,865/QALY gained P: 5.6-6.5 mg/dl: £123,831/QALY gained	For Policy 1 vs. Policy 2:§ CER: $29,050.27, 118,436.44; 52,322.05; 35,952.98/LY gained for lifetime, 2, 5 and 10 years respectively ICER: $48,786.75; 205,649.56; 88,458.49; 60,445.05/QALY gained for lifetime, 2, 5 and 10 years respectively ICER in Subanalysis (lifetime horizon): P>7.9 mg/dl: $17,413.39/QALY gained P: 6.6-7.8 mg/dl: $30,919.25/QALY gained P: 5.6-6.5 mg/dl: $241,333,839/QALY gained	One-way sensitivity analysis: Results were not sensitive when most of the uncertain model parameter values are changed. Results were sensitive to: P: 5.6-6.6 mg/dl; low utility of ESRD; including only patients with Block sig. increased RR of mortality; drugs costs; Discount rates (6%) Probabilistic sensitivity analysis: NR Structural sensitivity analysis: Using non-aggregated Block estimate (RR of mortality): 10% increase in the cost/QALY

Authors & Year	Population	Comparator	Main Results (ICER)	Adjusted ICER in $ for 2013 (Index, 2010=100)	Sensitivity Analysis
Dasgupta, 2013 [28] (NICE Clinical Guideline 157: Appendix F [29])	Prevalent patients Mean P (mg/dL): 7.09±1.55	CC, CA, SH and LC, as first- and second-line therapies	First-line therapy: CA: £8,197/QALY gained SH: £87,916/QALY gained LC: extendedly dominated Second-line therapy: CC (no switch): reference CA (no switch): £8,197/QALY gained CA->SH: £38,078/QALY gained CC->LC; CC->SH; LC (no switch); SH (no switch): dominated CA->LC: extendedly dominated ICER in Subgroup analysis in second-line therapy: ≥65 years: CC (no switch): reference CA (no switch): £6,441/QALY gained CA->LC: £43,778/QALY gained CA->SH: £54,193/QALY gained SH (no switch): £3,239,076/QALY gained CC->LC; CC->SH; LC (no switch): dominated	First-line therapy:‡ CA: $11,817.74/QALY gained SH: $126,749.8/QALY gained LC: extendedly dominated Second-line therapy: CC (no switch): reference CA (no switch): $11,817.74/QALY gained CA->SH: $54,897.62/QALY gained CC->LC; CC->SH; LC (no switch); SH (no switch): dominated CA->LC: extendedly dominated ICER in Subgroup analysis in second-line therapy: ≥65 years: CC (no switch): reference CA (no switch): $9,286.086/QALY gained CA->LC: $63,115.39/QALY gained CA->SH: $78,130.85/QALY gained SH (no switch): $4,669,824/QALY gained CC->LC; CC->SH; LC (no switch): dominated	One-way sensitivity analysis: Results were not sensitive when most of the uncertain model parameter values are changed. Probabilistic sensitivity analysis: NR
Goto, 2011 [31]	Prevalent hyperphosphatemic patients	Additive LC vs. conventional treatment (SH, CC and Ca lactate), as second-line therapy	For LC vs. Conventional treatment: $34,896/QALY gained	For LC vs. Conventional treatment:$33,396.87/QALY^	One-way sensitivity analysis: Results were not sensitive to changes in various key parameters Results were sensitive to: ↓effect of LC on CVD incidence and mortality by 40%, 60% and 80%; Including dialysis cost Probabilistic sensitivity analysis: Based on a WTP of $50,000/QALY gained, additive LC showed a 97.4% probability of being cost-effective compared with conventional treatment

Authors & Year	Population	Comparator	Main Results (ICER)	Adjusted ICER in $ for 2013 (Index, 2010=100)	Sensitivity Analysis
Huybrechts, 2005 [32]	Prevalent hyperphosphatemic patients	SH vs. CA, as first-line therapy for 1 year	For SH vs. CA: $1,641/LY gained ($2219/discounted LY gained) and $4448/CV event prevented	For SH vs. CA: $2,872.596/discounted LY gained and $5758.13/CV event prevented	One way sensitivity analysis: Results were not sensitive to changes in various parameters. Results were sensitive to: time horizon (2, 3, 4 and 12 years onward); including future costs; impact of treatment on cardiac calcification; initiating treatment when LDL-cholesterol >100 mg/dL Probabilistic sensitivity analysis: The likelihood of SH being cost-effective is 51% and 95% for CER ceiling of $2500 and $10,000/discounted LY gained, respectively
Huybrechts, 2009 [34]	Prevalent hyperphosphatemic patients	SH vs. CC as first-line therapy for 1 year	For SH vs. CC: CAD$12,384/discounted LY gained	For SH vs. CC: $12,162.78/discounted LY gained	One way sensitivity analysis: Results were not sensitive to changes in various parameters. Results were sensitive to: time horizon (≤5 years); efficacy of SH Probabilistic sensitivity analysis: The likelihood of SH being cost-effective is AROUND 50% and 95% for CER ceiling of CAN$7500 and CAN$15,000/discounted LY gained, respectively (DATA FROM THE GRAPH)

Authors & Year	Population	Comparator	Main Results (ICER)	Adjusted ICER in $ for 2013 (Index, 2010=100)	Sensitivity Analysis
Manns, 2007 [35]	Patients representative of typical Canadian dialysis patients	SH vs. CC, as first-line therapy	For SH vs. CC: Model 1 (primary): CAN$157,500/QALY gained Model 2 (CMA): S dominated Model 3 (mortality over time: first 2 years vs. ≥3 years): CAN$127,000/QALY gained Model 4 (mortality/age: <65 vs. ≥65 years): CAN$278,100/QALY gained <u>Subgroup analysis:</u> ≥65 years: CAN$105,500/QALY gained ≥55 years: CAN$102,700/QALY gained ≥45 years: CAN$97,000/QALY gained	For SH vs. CC: Model 1: $157,760.2/QALY gained Model 3: $127,209.9/QALY gained Model 4: $278,559.6/QALY gained <u>Subgroup analysis:</u> ≥65 years: $105,674.3/QALY gained ≥55 years: $102,869.7/QALY gained ≥45 years: $97,160.28/QALY gained	<u>Scenario analyses:</u> Exclusion of dialysis and transplantation-related health care costs: CAN$43,800-$1868,00/QALY gained (Models 1, 2, 3). Excluding the costs of dialysis and transplantation and including only patients ≥65 (Model 4): $23,300/QALY gained (unrealistically optimistic estimate of the cost-effectiveness of SH). US scenario: SH vs. CC: $156,700/QALY gained; SH vs. CA: $175,000/QALY gained DCOR-specific scenario: SH vs. CC: $179,200/QALY gained; SH vs. CA: $205,000/QALY gained <u>One-way sensitivity analysis:</u> Results were robust to clinically plausible changes in all uncertain variables <u>Probabilistic sensitivity analysis</u> Significant uncertainty in the true cost-effectiveness of SH: the likelihood that the use of SH would be cost-effective is 15 and 32% for a WTP of CAN$50,000 or $100,000/QALY gained (Model 1). For the subgroup of patients ≥65 years, the probability that the use of SH would be cost-effective is 21 and 44% for a WTP of CAN$50,000 or $100,000/QALY gained, respectively.

Authors & Year	Population	Comparator	Main Results (ICER)	Adjusted ICER in $ for 2013 (Index, 2010=100)	Sensitivity Analysis
Park, 2011 [37]	Prevalent hyperphosphatemic patients	LC vs. SH, as first-line therapy (after previous treatment with CBB)	For LC vs. SH: ITT population: ICER: $24,724/QALY gained and $15,053/LY gained (life expectancy alone considered) Completer population: ICER: $15,285/QALY gained and $9,337/LY gained	For LC vs. SH: ITT population: ICER: $26,834.59/QALY gained and $16,338.01/LY gained Completer population: ICER: $16,589.82/QALY gained and $10,134.06/LY gained	<u>One-way sensitivity analysis:</u> Results were robust within the range of plausible assumptions in the model for ITT and completer populations Results were sensitive to: LC costs <u>Probabilistic sensitivity analysis:</u> The likelihood that the use of LC would be cost-effective is 61.9% and 85.5% for a WTP of $50,000 for the ITT and completer population respectively.
Ruggeri, 2014 [39]	Incident patients P (mg/dL): S: 5.6(1.7); CC: 4.8(1.4)	SH vs. CBB (although not required by the protocol, all patients received CC), as first-line therapy	For SH vs. CC: €4,897/LY gained	For SH vs. CC: $6,461.39/LY gained	<u>One way sensitivity analysis:</u> Results were sensitive to: Inclusion of dialysis costs <u>Probabilistic sensitivity analysis:</u> The likelihood that the use of SH would be cost-effective is 95 % at a WTP threshold of €10,000/LY gained (PS: ICER for SH vs. CC fell between a WTP threshold of €30,000 and €50,000/LY gained in 96.8 % of the bootstrap samples)
Taylor, 2008 [41]	Incident patients	SH vs. CC, as first-line therapy	For SH vs. CC: ICER: £27,120/QALY gained and £15,508/LY gained	For SH vs. CC: ICER: $47,152.9/QALY gained and $26,963.4/LY gained	<u>Deterministic sensitivity analysis:</u> Results were not sensitive to various parameters: time horizon (1 , 10 years); inclusion of dialysis costs; cost of drugs; RR of hospitalization for S vs. CBB; age ≥65 years; low utility of ESRD <u>Probabilistic sensitivity analysis</u>: NR

Authors & Year	Population	Comparator	Main Results (ICER)	Adjusted ICER in $ for 2013 (Index, 2010=100)	Sensitivity Analysis
Vegter, 2011 [43]	Incident hyperphosphatemic patients	LC vs. CBB (CC and CA), as second-line therapy (Patients not responding to CBB with (P>5.5 mg/dl) received a trial with LC. Patients not responding to LC (P>5.5 mg/dl) returned to CBB	For LC vs. CBB: ICER: £6,900/QALY gained (90% probability interval: 5,500–8,800) and £4,200/LY gained (90% probability interval: 3,400-5,300)	For LC vs. CBB: ICER: $11,461.06/QALY gained (90% probability interval: 9,135.62-14,617) and $6,976.29/LY gained (90% probability interval: 5,647.47-8,803.42)	Sensitivity analysis: Results were robust to plausible variations in several model parameters Results were sensitive to: inclusion of future unrelated dialysis costs; time horizon: for 2, 5, 10 and 20 years Probabilistic sensitivity analysis: NR
Vegter, 2012 [44]	Incident hyperphosphatemic patients	LC vs. CC, as second-line therapy	For LC vs. CC: ICER: CAN$13,200/QALY gained (90% probability interval: 3,000-25,100) and CAN$7,900/LY gained (90% probability interval: 1,800-14,600)	For LC vs. CC: ICER: $11,524.5/QALY gained (90% probability interval: 2,618.73-21,914.29) and $6,897.229/LY gained (90% probability interval: 1571.02-12,746.58)	Sensitivity analysis: Results were robust to most variations in model parameters Results were sensitive to: inclusion of future unrelated dialysis costs; time horizon of 2 years; LC drug price; utility of dialysis Probabilistic sensitivity analysis: The ICER of LC vs. CC was well below the commonly accepted Canadian WTP threshold of CAN$50,000/QALY gained (PROBABILITY OF ALMOST 99%; DATA FROM FIGURE 4)

§: ICER: converted from 2004 British Pounds; ‡: ICER: converted from 2012 British Pounds; ^: ICER was re-estimated using appropriate PPP for 2010 and then up-rated to 2013, using CPI: $1= ¥111.59 Japanese Yen

ICER: incremental cost-effectiveness ratio; S: sevelamer; CBB: calcium-based binders; CA: calcium acetate; CC: calcium carbonate; QALY: quality-adjusted life year; LY: life-year; NR: not reported; LC: lanthanum carbonate; P: phosphorus; ESRD: end-stage renal disease; RR: relative risk; SH: sevelamer hydrochloride; Ca: calcium; CVD: cardiovascular disease; WTP: willingness to pay; CV: cardiovascular; LDL: low-density lipoprotein; CMA: cost-minimization analysis; ITT: intention-to-treat; PPP: purchasing power parity; CPI: consumer price index

CHAPTER

3

A SOCIETAL COST-OF-ILLNESS STUDY OF HEMODIALYSIS IN LEBANON

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ABSTRACT

Aim: Renal failure is a growing public health problem, and is mainly treated by hemodialysis. This study aims to estimate the societal costs of hemodialysis in Lebanon.

Methods: This was a quantitative, cross-sectional cost-of-illness study conducted alongside the Nutrition Education for Management of Osteodystrophy trial. Costs were assessed with a prevalence-based, bottom-up approach, for the period of June-December 2011. The data of 114 patients recruited from 6 hospital-based units were collected through a questionnaire measuring health care costs, costs to patients and family, and costs in other sectors. Recall data were used for the base-case analysis. Sensitivity analyses employing various sources of resources use and costs were performed. Costs were uprated to 2015US$. Multiple linear regression was conducted to explore the predictors of societal costs.

Results: The mean 6-month societal costs were estimated at $9258.39. The larger part was attributable to heathcare costs (91.7%), while costs to patient and family and costs in other sectors poorly contributed to the total costs (4.2% and 4.1%, respectively). In general, results were robust to sensitivity analyses. Using the maximum value for hospitalization resulted in the biggest difference (+15.5% of the base-case result). Female gender, being widowed/divorced, having hypertension comorbidity, and higher weekly time on dialysis were significantly associated with greater societal costs.

Limitations: Information regarding resource consumption and cost were not readily available. Rather, they were obtained from a variety of sources, with each having its own strengths and limitations.

Conclusion: Hemodialysis represents a high societal burden in Lebanon. Using extrapolation, its total annual cost for the Lebanese society is estimated at $61,105,374 and the mean total annual cost ($18,516.7) is 43.70% higher than the gross domestic product per capita forecast for 2015. Measures to reduce the economic burden of hemodialysis should be taken, by promoting chronic kidney disease's prevention and encouraging transplantation.

KEYWORDS

Costs and cost analysis; cost of illness; hemodialysis; Lebanon.

INTRODUCTION

Renal failure is an emerging global public health problem [1–4], and hemodialysis (HD) is its main treatment modality [3,4]. As the prevalence of renal failure continues to escalate, the need for HD is also increasing in both developed and developing countries [5,6].

Although a life-saving therapy, HD poses a heavy burden on the patients [7,8]. It requires attending a 3-5-hour treatment session 3-times a week, adhering to a wide range of dietary restrictions and complex medications regimens. HD patients are at increased risks of mortality [9], morbidity, and hospitalization [10,11]. They have lower quality-of-life compared with the general population [12] and with patients treated with other renal replacement therapies (RRT) [13]. HD also results in an increased long-term mental, emotional, and physical burden on HD patients' caregivers, and adversely affects their quality-of-life [14].

HD is the leading resource-consuming RRT [15–17], and its medical expenditures pose a significant burden on national health systems [17–19]. In 2003, in Jordan, the overall expenditure on HD was ≈ US$30 million, approaching 4% of the total health expenditures, which is disproportionately greater than the 0.03% prevalence of this patient population [20]. HD is also costly in terms of patient and family costs. Although productivity losses for HD patients, their families or caretakers have been rarely assessed and incorporated into economic evaluations, recent literature highlights this component as a cost driver for HD. In India, 24.4% of total HD costs was attributed to productivity losses due to entering the dialysis procedure [21]. Similar figures were reported from Chile, where patients’ loss of productivity and unemployment contributed to 28.5% of total HD costs [22]. HD is also costly in terms of costs in other sectors. In England in 2010, an annual cost of £26,835 has been estimated for each patient’s journeys to HD centers [17].

Knowing its increasing prevalence and high cost, HD needs to be addressed by specific healthcare policies. Estimating the financial burden of HD and exploring its dimensions and drivers are first required in order to assist public health policy-makers in making informed planning and budgeting decisions. Cost-of-illness (COI) studies assess the economic burden of a particular health problem over a defined period of time. These studies intend to draw the public’s attention to particular health problems while providing useful information to foster policy debate. COI studies inform planning of healthcare services, evaluation of policy options and prioritization of research [23].

Just et al. [15] and Mushi et al. [18] systematically reviewed published cost of dialysis (peritoneal dialysis and HD) studies. These reviews highlighted the methodological flaws and differences across studies and pinpointed the scarcity of studies adopting a societal perspective. They concluded that the cost drivers and costs of HD vary widely among countries and between authors in the same country and recommended additional research, particularly in developing countries. Between-country differences were also highlighted by Ranasinghe et al. [24], where the reported annual expenses per HD patient varied from US$3,423 in India to US$77,506 in the US. No studies conducted in Lebanon were identified in these reviews.

In Lebanon, in 2015, 3300 patients were receiving HD in 64 hospital-based units. According to the National Kidney Registry (NKR) of Lebanon, the prevalence of HD has grown by 33% between 2007 and 2012 (570 to 700 patients per million people, respectively), compared to an increase of 5% in the Lebanese population during the same period. This was mainly due to improved diagnosis and providing renal replacement therapy to older patients [25]. Up to-now, no previous studies have addressed the financial impact of HD on the Lebanese society or explored the main cost drivers in this patient population. This study aims, therefore, to estimate, in a representative sample of Lebanese adult patients, the 6-month costs of HD, from a societal perspective.

METHODS

The current study is a multi-center, retrospective, bottom-up (referring to patient recall/records), prevalence-based COI estimate. It was conducted alongside the Nutrition Education for Management of Osteodystrophy (NEMO) trial, the protocol of which is detailed in Karavetian et al. [26]. In brief, NEMO is a multi-center randomized controlled trial in Lebanese hospital-based HD units. NEMO explored the effectiveness of intensive nutritional education on the management of the Chronic Kidney Disease- Mineral Bone Disorder (CKD-MBD) among Lebanese adult HD patients. Twelve hospital-based HD unites were randomly recruited to the NEMO trial from the official list of hospital-based HD units in Lebanon. These units were randomly assigned to two clusters: (1) cluster A (6 units) and (2) cluster B (6 units). Cluster A patients were then randomly assigned according to their HD shifts into two protocols: (1) Dedicated Dietitian (intervention group) and (2) Existing Practice (control group). Cluster B patients were assigned to the Trained Hospital Dietitian protocol (partial intervention group). The COI analysis was carried out in the units randomly recruited to the control group. These six units were receiving care following existing practice (control group). NEMO was conducted according to the guidelines of the Declaration of Helsinki and all procedures involving human subjects were approved by the institutional review board of each participating institution [26].

SUBJECTS AND PROCEDURE

Eligible patients were those being treated in HD units recruited to the study. They had to be Lebanese, adults (≥18 years), stable (free of the following diseases: cancer, infection with the

Human Immunodeficiency Virus and hepatitis), and on HD for ≥6 months. Eligible patients had also to be capable to communicate either verbally or through writing. They had to be willing to participate and sign the consent form. Eligible subjects were approached for participating in the study. Those who did not meet the inclusion criteria listed above were excluded.

Data collection was through face-to-face interviews with HD patients, during HD sessions. Data were collected retrospectively for the period between June and December 2011, at one time-point (January 2012: end of intervention phase). Recall data were used for the base-case analysis.

COST PERSPECTIVE

The study adopted a societal perspective; accordingly, all costs that burden society were accounted for, whenever possible. The societal perspective incorporates all costs regardless who incurs them [27]. The COI followed 3 steps: identification, measurement and valuation.

Step I: Identification of costs

Included costs were those related to HD, its consequences and treatment and were categorized as (1) health care sector costs: costs of maintenance HD and pertaining services, such as nephrologist consultation (provided each session), nursing services, laboratory procedures, basic solutions to provide dialysis, administrative materials, costs of equipment, and expenses for the dialysis room..., emergency HD, hospitalization, medications, specialist physician- other than nephrologist, i.e. cardiologist, neurologist, gastroenterologist…, dietitian and psychologist consultations, and integrated home care provided by physicians or nurses; (2) costs to patient and family, such as caregiver costs and productivity losses; and (3) costs in other sectors: travel costs [28].

Step II: Measurement of costs

A resource utilization questionnaire was developed in English for measuring cost items. The questionnaire included questions on sociodemographic characteristics, health services and other services' utilization. It was designed by the research team to meet the condition of Lebanese HD patients. This was done because different disease areas, health care systems and cultural specificities affect health care and other resources use. Finally, the questionnaire was translated to Arabic and pilot-tested on 20 adult Lebanese HD patients. The feedback from the pilot was taken into consideration in the final version of the questionnaire (Appendix 1).

Step III: Valuation of costs (Table 1)

The costs were gathered and calculated in Lebanese pounds (L.L.), converted to US$ (1 US$=1507.5 L.L.; year of reference: 2011) [29] and uprated to 2015US$ using Consumer Price Indices (Index, 2010=100) [30]. A macro-costing valuation was applied, whereby composite intermediate resources (e.g. inpatient day, HD session...) were identified and measured. For the base-case and sensitivity analyses, the mean reported costs incurred by patients were used to value costs of the following resources: HD and emergency HD, consultations with health care professional, hospitalizations and professional care. The cost of drugs were derived from the Lebanese National Drug Index for the year 2011 [31]. Valuation of informal care was based on the proxy good method [32] and the valuation of productivity losses were based on the human capital approach [33]. The mean quantity/frequency of use of each service was multiplied by its respective mean unit cost to obtain the total costs. The total costs for all patients were divided by the number of included patients in order to estimate the mean cost per patient for the 6-month period.

SENSITIVITY ANALYSES

In order to test the robustness of our results, three sensitivity analyses were conducted. The first analysis used the minimum and maximum costs reported by the patients for the main cost drivers. We calculated first the total costs for each modified cost, i.e. minimum and maximum costs for each item separately, and then for all modified costs combined, thus allowing us to obtain the lowest and highest estimates. In the second analysis, we used information collected from the questionnaire for resources use but estimated resources costs using information collected from key informants from the Lebanese Ministry of Public Health, the Lebanese Ministry of Labor, the Lebanese Society for Nephrology and Hypertension, the Syndicate of Hospitals and third party payers in Lebanon. For the third analysis, we used information collected from the patients' medical charts regarding use of health care resources and costs collected from key informants for resources costs valuation. Resources costs pertaining to the base-case and sensitivity analyses are available in Appendix 2.

Table 1. *Cost measurement and valuation (2015 US$)*

	Unit	Cost		
		Base-case analysis	Sensitivity analysis	
			Minimum	Maximum
Health care sector costs				
HD				
HD	Session	97.90	94.32	103.05
Emergency HD	Session	97.90	94.32	103.05
Health care professionals				
Specialist physician	Contact	52.80	20.96	153.70
Dietitian	Contact	NA	NA	
Psychologist	Contact	34.92	NA	
Medications	Various	Various	NA	
Hospitalization	Day	189.25	22.70	702.19
Professional home care	Hour	24.45	10.13	52.66
Costs to patient and family				
Informal care	Hour	1.67	NA	2.18
Productivity losses	Day	Various	NA	
Costs in other sectors				
Travel	Trip	2.79	NA	

HD: hemodialysis

STATISTICAL ANALYSIS

Descriptive analysis of the patients' characteristics, consumption of different resources and different costs were performed using SPSS, version 21. For the sensitivity analysis, the mean difference with the base-case analysis results was calculated. Missing data for resources use (volume) were replaced by the mean value reported by the patients of the same HD unit. This was done because the nephrologists usually adopt common practice guidelines and treatment protocols for patients treated in the same unit.

Forward multiple linear regression analysis was performed to determine predictors of societal costs. We used a set of predictors capturing socio-demographic (age, gender, work status, social status) and clinical characteristics (vintage, HD time per week, malnutrition inflammation score (MIS), diabetes comorbidity, hypertension comorbidity and cardiovascular disease comorbidity). As a first step, we assessed through a bivariate analysis, the association between societal costs and each of the above-mentioned variables. Independent t-test, one-way ANOVA and Pearson correlation were used. Variables with statistical significance <0.2 were included in the forward multiple linear regression analysis (age, gender, social status, HD time per week, MIS, hypertension comorbidity). Adjusted R^2 was calculated to provide information about the variance in societal costs explained by the complete model. The results were presented as standardized (β) coefficients. $p<0.05$ was considered statistically significant.

RESULTS

PARTICIPANTS' CHARACTERISTICS

Of 133 participants (already enrolled in the NEMO trial) that were approached to participate in the COI analysis, 119 agreed to participate (89%). A total of 114 provided complete responses to the questionnaire and were included in our analysis. The final sample consisted of 63 males and 51 females, with a mean age of 60.25 years. 47.4% of the sample were older than 64 years (complete). Only 17.5% of the sample were employed at the time of the analysis. The others were either unemployed (38.6%) or retired (43.9%). On average, patients were on dialysis for 47.82 months and had 9.51 hours of dialysis per week. Their mean MIS was normal (7.90). Patients' characteristics are further displayed in Table 2.

Table 2. *Patients characteristics (n=114)*

Socio-demographic characteristics	**N (%)**
Gender, Male	63 (55.3)
Social status	
Single	14 (12.3)
Married	93 (81.6)
Widowed	7 (6.1)
Educational level	
Illiterate	25 (21.9)
Read and write	19 (16.7)
Elementary	30 (26.3)
High school	22 (19.3)
University	18 (15.8)
Employment status, Employed	20 (17.5)
	Mean (SD)
Age (years)	60.2 (14.3)
Clinical characteristics	**N (%)**
Primary cause of HD initiation	
Diabetes	20 (17.5)
CVD, HTN	17 (14.9)
Renal diseases	43 (37.7)
Other	34 (29.8)
Co-morbidities	
Diabetes	41 (36.0)
HTN	76 (66.7)
CVD	24 (21.1)
	Mean (SD)
HD vintage (months)	47.82 (49.38)
HD time/week (hours)	9.50 (2.71)
MIS	7.90 (3.53)

SD: standard deviation, HD: hemodialysis, CVD: cardiovascular disease, HTN: hypertension, MIS: malnutrition inflammation score

RESOURCES USE

On average, patients underwent 67.76 sessions of HD during the assessed 6 months. During this period, few patients reported contacts with health care professionals, with the exception of specialist physician (23.7%). Nevertheless, specialist physician-patient contact was low, with less than 1 contact on average in the past 6 months. Use of professional home care was also minimal (1.8%). Most commonly used drugs were calcium carbonate (78.9%), intravenous (IV) iron (70.2%), erythropoietin (EPO) (64.9%) and vitamin B complex (53.5%). 35.1% of patients were hospitalized during the past 6 months, with a mean length of stay of 2.82 days. Almost half (47.4%) of the patients reported receiving care from their family or friends (informal care), with an average of 117.01 hours being dedicated to care for them in the past 6 months. During the same period, 47.4% of the patients reported being unable to perform daily activities (paid and unpaid labor) due to HD, with a mean of 94.75 lost labor hours. Resources use during the 6- month period is detailed in Table 3.

SOCIETAL COSTS

The societal costs for each patient were estimated at US$9258.39 over a period of 6 months, with health care costs accounting for 91.73% of this cost. The biggest part of the total costs was attributed to regular HD, at US$6632.68 per patient per 6 months (71.64% of societal costs). Medications accounted for the second biggest cost (13.67%), with US$1264.31 per patient per 6 months. EPO, IV Iron and Sevelamer were the most costly medications (US$870.24, US$134.20 and US$109.26 per patient per 6 months, respectively). The third biggest cost was attributed to hospitalization, with a mean of US$532.90 per patient per 6 months. Costs to patients and family and those in other sectors (transportation) poorly accounted to the total costs (4.18% and 4.09%, respectively) (Table 4).

Table 3. *Resources use during the 6-month period (n=114)*

		Users		Resource use per patient (users and non-users)				
	Unit	**N**	**%**	**Min**	**Max**	**Median**	**Mean**	**SD**
Health care sector costs								
HD								
HD	Session	114	100	52.00	105.00	78.00	67.75	13.25
Emergency HD	Session	21	18.4	0.00	8.00	0.00	0.38	1.03
Health care professionals								
Specialist physician	Contact	27	23.7	0.00	6.00	0.00	0.44	1.00
Dietitian	Contact	0	0.0	0.00	0.00	0.00	0.00	0.00
Psychologist	Contact	1	0.9	0.00	5.00	0.00	0.04	0.47
Medications								
Calcium Carbonate	Tablet	90	78.9	0.00	2745.00	366.00	474.00	438.78
Calcium Acetate	Tablet	40	35.1	0.00	1647.00	0.00	236.62	389.47
Sevelamer	Tablet	27	23.7	0.00	1098.00	0.00	75.13	161.89
Cinacalcet	Tablet	0	0.0	0.00	0.00	0.00	0.00	0.00
Active Vitamin D*	Various	50	43.9	0.00	360.00	0.00	20.44	45.04
Vitamin D	Capsule	27	23.7	0.00	180.00	0.00	9.19	29.79
Vitamin B complex	Injectable Solution	61	53.5	0.00	5490.00	461.48	785.13	1070.03
Iron IV	Injectable Ampoule	80	70.2	0.00	72.00	12.00	13.87	14.47
Iron	Tablet	38	33.3	0.00	360.00	0.00	36.48	71.15
EPO**	Various	74	64.9	0.00	288000.00	96000.00	127190.28	116895.02
Hospitalization	Day	40	35.1	0.00	25.00	0.00	2.82	5.25
Professional home care	Hour	2	1.8	0.00	1.00	0.00	0.02	0.13
Costs to patient and family								
Informal care	Hour	54	47.4	0.00	1008.00	0.00	117.01	262.71
Productivity losses	Hour	54	47.4	0.00	736.00	0.00	94.75	186.49
Costs in other sectors								
Travel	Trip	114	100	104.00	208.00	156.00	135.47	26.45

Min: minimum, Max: maximum, SD: standard deviation, HD: hemodialysis, IV: intravenous, EPO: erythropoietin
**Resources use unit was mcg (microgram); **Resource use unit was UI (International Unit)*

Table 4. *Costs per patient during the 6-month period (n=114) (2015 US$)*

	Mean cost	% of total costs	Median cost
Health care sector costs			
HD			
HD	6632.68	71.64	7636.64
Emergency HD	37.58	0.41	0.00
Total	***6670.27***	***72.05***	***7636.64***
Health care professionals			
Specialist physician	23.16	0.25	0.00
Dietitian	0.00	0.00	0.00
Psychologist	1.53	0.02	0.00
Total	***24.69***	***0.27***	***0.00***
Medications			
Calcium Carbonate	60.77	0.66	46.92
Calcium Acetate	39.37	0.43	0.00
Sevelamer	109.26	1.18	0.00
Cinacalcet	0.00	0.00	0.00
Active Vitamin D	15.54	0.17	0.00
Vitamin D	4.82	0.05	0.00
Vitamin B complex	21.78	0.24	12.80
Iron IV	134.20	1.45	116.14
Iron	8.32	0.09	0.00
EPO	870.24	9.40	675.50
Total	***1264.31***	***13.67***	***1315.28***
Hospitalization	532.90	5.76	0.00
Professional home care	0.43	0.005	0.00
Total	***8492.61***	***91.73***	***8439.30***
Costs to patient and family			
Informal care	196.52	2.12	0.00
Productivity losses	190.64	2.06	0.00
Total	***387.16***	***4.18***	***131.00***
Costs in other sectors			
Travel	378.62	4.09	435.99
Total	***378.62***	***4.09***	***435.99***
Total societal costs	***9258.39***	***100***	***9201.22***

SD: standard deviation, Min: minimum, Max: maximum, HD: hemodialysis, IV: intravenous, EPO: erythropoietin

SENSITIVITY ANALYSES

As detailed in Table 5, using minimal and maximal reported values for hemodialysis, hospitalization and specialist physician consultation resulted in societal costs close to those found in the base-case analysis. When compared with the base-case results, the biggest differences were caused by changes in hospitalization costs (differences in the mean costs per patient were +US$1443.90 and US$-469.39, for the maximal and minimal fees, respectively).

Using other sources for estimating resources use and costs resulted in almost similar results to those of the base-case analysis. Using the costs obtained from key informants, the societal costs were US$8964.03 per patient per 6 months (3.17% lower than the value obtained in the base-case analysis). Using health care resources use obtained from the patients' medical charts, and the costs obtained from key informants, the analysis resulted in societal costs of US$9273.56 per patient per 6 months (0.16% higher than the value obtained in the base-case analysis).

Table 5. *Sensitivity analyses (Costs per patient during the 6-month period in 2015 US$)*

	Mean total costs	Difference from the mean costs obtained in the base-case analysis	
	2015 US$	**2015 US$**	**%**
Analysis 1			
Different costs			
Hemodialysis			
Minimum	9014.00	-244.38	-2.63%
Maximum	9609.03	350.640	+3.78%
Hospitalization			
Minimum	8789.00	-469.39	-5.06%
Maximum	10702.30	1443.90	+15.59%
Specialist physician consultation			
Minimum	8829.27	-429.11	-4.63%
Maximum	9653.28	394.89	+4.26%
Highest estimate	11097.62	1839.23	+19.86%
Lowest estimate	8531.07	-727.31	-7.85%
Analysis 2			
Costs from key informants	8964.03	-294.35	-3.17%
Analysis 3			
Resources use from medical charts and costs from key informants	9273.56	15.170	+0.16%

PREDICTORS OF SOCIETAL COSTS

The best model retained HD time per week, gender, social status and hypertension comorbidity as predictors of the variability in societal costs. The model accounted for 56.2% of the variability in societal costs and for 54.2% when adjusted for the number of predictors. Female gender was significantly associated with greater societal costs (US$9798.80 vs. US$8820.91 for males). Being widowed or divorced also predicted greater societal costs (US$11190.38 vs. US$9168.48 and US$8889.66 for single and married, respectively). Having hypertension as comorbidity also significantly contributed to greater societal costs (US$9835.49 vs. US$8104.20). Finally, greater weekly time on HD (necessitating more HD sessions per week) was significantly associated with greater societal costs (Table 6).

Table 6. *Predictors of societal costs of hemodialysis*

Predictor	Standardized Coefficients	p	95.0% Confidence Interval	
			Lower Bound	Upper Bound
HD time per week	0.65	<0.001	579.34	907.96
Gender (female)	0.19	<0.001	269.43	1588.57
Social status (widowed or divorced)	0.17	0.01	180.27	1645.61
Hypertension comorbidity	0.14	0.04	8.26	1490.73

HD: hemodialysis

DISCUSSION

To our knowledge, this is the first COI study on HD conducted in Lebanon. The 6-months societal cost per HD patient was estimated at US$9258.39 for the year 2015, with the largest part (91.73%) being attributed to health care costs, estimated at US$8,492.61. In comparison with the Gross Domestic Product (GDP) per capita of US$10,424.28 forecast for 2015 [34], the mean annual cost per HD patient ($US18,516.7) was 43.70% higher.

The study sample was similar to the general HD population in Lebanon described by the NKR in 2012 [25] in many sociodemographic aspects, such as age (60.2±14.3 in our sample vs. 59.4±16.2 in the general HD population), gender (males: 55.3% vs. 56.8%), educational level (illiteracy: 21.9% vs. 23.4%). Employment was slightly lower in our sample than in the general population (17.5% vs. 23.6%, respectively). As for the clinical characteristics, kidney diseases were the cause of end stage renal disease in both groups (37.7% vs. 42%). Both groups have hypertension and diabetes as comorbidity (66.7% vs. 57.8%; and 36% vs. 29.2%, for our sample and the general HD population, respectively). Nevertheless, HD vintage was shorter in our sample (47.82±49.38 vs. 58.6±61.3 months). Assuming that 3,300 patients are currently being treated by HD, the total annual cost for the Lebanese society would therefore be US$61,105,374, with an estimated total annual health care cost US$56,051,226. Accordingly, ≈ 1.82% of the total health expenditure in Lebanon in 2012 (US$3,083,009,900.8) [35] would be spent on HD patients, who actually represent less than 0.1% of the total Lebanese population. All these factors pinpoint HD as a great economic burden to the health system in the country. These results are of utmost importance for health care payers in Lebanon, especially the MOPH, since it covers the cost of therapy for around 55% of HD patients in the country and for whom, about 8% of the Ministry's budget is allocated [25].

Interestingly, productivity losses only contributed to 2.06% of the total cost. Although this cost component has been rarely assessed in COI studies on HD, the proportion found in this study is greatly lower than what was reported from other countries [21,22,36,37]. Beside differences in measurement and valuation methods, this finding might be attributed to the fact that 82.5%

of the patients in our study were already unemployed or retired at the time of the analysis. Moreover, being prevalent patients, they already adapted their work schedules and daily life activities to their HD treatment, and the majority of them eventually managed to avoid losing additional hours of work or daily life activities due to their illness and its treatment. Furthermore, the resulting low number of lost work hours might be attributed to the fact that we only estimated productivity losses during the past 6-month and we did not directly collect information about whether the patients were unemployed due to their renal disease. The direct comparison of the cost of HD in Lebanon with the costs reported from neighboring countries is challenging, because of the differences in the costs included and the methodological disparities when measuring and valuing costs. Arefzadeh et al. [36] estimated the annual societal cost of HD in Iran to be US$13,201.81 per patient (uprated to 2015US$). However, the authors followed a different taxonomy for costs and did not clearly report the method used for valuing some of the included costs. Transportation and absence from work (28.9%), staffs (21.5%) and treatment instruments (21.1%) costs constituted the largest part of the total costs. In Jordan, published COI studies reported some different results. In Al-Shdaifat and Manaf [38], the annual societal cost per patient uprated to 2015US$ were US$10,843.91 (direct medical cost: 41%; direct non-medical cost: 11% and indirect cost: 48%), whereas in Batieha et al. [20] the direct annual cost per patient cost rose to US$22,367.67. Despite using a different categorization of costs in the first study, data collection was conducted in a similar way to the one used in this analysis. However, costs related to premature death were included which might explain the differences found in the contribution of productivity losses between the study by Al-Shdaifat and Manaf [38] and our study. No ample information were provided in Batieha et al. [20] to enable investigation of the reasons behind the differences between this study and ours.

On the other hand, our study might have underestimated the total HD costs incurred by the Lebanese society since the costs of drugs related to co-morbidities, such as insulin for the treatment of diabetes, or anti-hypertensive medications for the treatment of high blood pressure, were not measured and included in the analysis.

The current study faced several challenges. Information regarding resource consumption and cost were not readily available. Rather, they were obtained from a variety of sources (patient recall, patients' medical charts and key informants), with each having its own strengths and limitations. Reactivating the NKR, having cost databases and national cost estimates of HD is thus recommended to facilitate future COI and economic evaluation studies. Having a manual for cost analysis in health care research in Lebanon would also facilitate a more accurate and systematic way for conducting future COI studies in the country. On the other hand, this analysis has several strengths. First, it was a multicentric study, thus enabling the generalizability of its findings to the HD population in Lebanon. Second, we used a societal perspective, thus providing a holistic view on the economic burden of HD to the Lebanese society. Third, we relied on a bottom-up approach for costing, which is considered preferable in terms of estimating costs for chronic patients [39]. Finally, our findings were robust to several sensitivity analyses. Our study is subject to several limitations as well. First, we used a self-reported questionnaire to estimate health care consumption. This may cause recall bias, although available evidence indicate that questionnaire design and respondent motivation were more influential on recall bias than the period of recall [40]. Second, patients with limited cognitive skills may have troubles understanding the questions. In an attempt to overcome these two limitations, the resource utilization questionnaire used in this study was designed following good practices for improved accuracy in resource use estimation [41]. Third, we relied on information collected from patients to value the costs of resources. This was done because there is no manual for cost analysis in health care research in Lebanon. Finally, differences in funding of health care systems, in dialysis modality utilization, and other cost estimation techniques limit the accuracy of the comparison of our results with other countries.

Reducing the economic burden of HD could be achieved by decreasing the number of patients requiring this treatment. Preventing the progression of renal disease is one suggested option. In Lebanon, the most frequent causes of renal failure are diabetes mellitus, hypertension and kidney diseases [25]. Early detection, correct referral to specialists and adequate medical and dietetic management of these diseases [42–44] are essential for slowing progression to renal failure, delaying or even eliminating the need for RRT. These programs are of critical importance, since it is assumed based on extrapolation from international data that there are between 41,000 and 82,000 stage 3 and 4 CKD patients in Lebanon, and most of them are unaware of their condition [25,45]. On the other hand, increasing the use of live or cadaveric donor kidney transplantation could be another option. These RRT are considered to be the most cost-effective treatments for renal failure, offering considerable improvement in the patients' quality-of-life [46]. Efforts to foster the culture of organ donation through public education and awareness, increased support from religious leaders, and enhancement of government infrastructure and financial resources are recommended [47]. In the meantime, other cost-effective forms of RRT, such as home HD could be suggested. This type of treatment has shown to be cost-effective and is associated with better health outcomes for patient survival and quality-of-life [48–50].

CONCLUSION

This study pioneers in assessing the costs of HD in Lebanon from a societal perspective, and is one of the very first COI studies in the country. The economic burden of HD is high in Lebanon. The largest part of this burden is attributable to the regular HD treatment. Further studies in larger populations would be necessary to assess potential differences between different subgroups of this population. This paper presents detailed cost figures that could be used in future cost-effectiveness analyses in the Lebanese HD population, where very few, if any, economic evaluations are available. It is also hoped that the information generated from this report will be used as a pertinent advocate to justify the implementation of public health interventions and programs targeting the prevention of HD.

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Appendix 1: Resource utilization questionnaire

<table>
<tr><td>1</td><td>What is your insurance/3rd party payer?
□NSSF □ MOPH □ Army □COOP □Private □Other……………….</td></tr>
<tr><td>2</td><td>In the past 6 months, how often have you contacted a specialist physician (like a cardiologist &/or endocrinologist &/or surgeon &/or …….)?----------------------
How much did it cost per visit?-----------------------
How much of it did you pay from your pocket?-----------------------</td></tr>
<tr><td>3</td><td>In the past 6 months, how often have you contacted your dietitian?----------------------
How much did it cost per visit?-----------------------</td></tr>
<tr><td>4</td><td>In the past 6 months, how often have you contacted a psychologist?----------------------
How much did it cost per visit?-----------------------</td></tr>
<tr><td>5</td><td>In the past 6 months, how many nights have you spent in the hospital?----------
How much did it cost per day?--
How much of it did you pay from your own pocket? -------------------------------</td></tr>
<tr><td>6</td><td>In the past 6 months, how many times did you have to go for an extra emergency hemodialysis session? ---</td></tr>
<tr><td>7</td><td>List the number of medications that you are prescribed in the past 6 months
<table>
<tr><td></td><td>Calcium carbonate</td><td>Calcium acetate</td><td>Sevelamer</td><td>Cinacalcet</td><td>Vitamin D</td></tr>
<tr><td>How many pills per day</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>Active Vitamin D</td><td>Vitamin B complex</td><td>Iron Pills</td><td>IV iron</td><td>Erythro-poietin</td></tr>
<tr><td>How many pills per day</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
For which one of them did you pay from your own pocket (were not reimbursed) in the past 6 months?
____
____</td></tr>
<tr><td>8</td><td>In the past 6 months, how many hours per week on average did you need family/ friends to take care of you or help you due to your health situation?-----------------------
How much did it cost per hour?-----------------------</td></tr>
<tr><td>9</td><td>In the past 6 months, how many hours per week did you need home care professionals (paid help) like home nurses or home doctors….?
How much did it cost you?-----------------------</td></tr>
<tr><td>10</td><td>In the past 6 months, how many days were you unable to perform your daily activities due to your health (for example, days lost from work or school, days where you were unable to perform domestic work)?-----------------------</td></tr>
</table>

Appendix 2: Resources costs for the base-case and sensitivity analyses (2015 US$)

Resource	Valuation	
	Base-case analysis	**Sensitivity analysis**
Health care sector costs		
HD	The average cost of HD by third party payers (US$97.90) by the number of regular and emergency HD sessions.	Minimal (US$94.32) and maximal (US$103.05) costs of HD session reported by health care payers in Lebanon multiplied by the number of regular and emergency HD sessions.
Health care professionals	The average cost per contact reported by the patients multiplied by the reported number of health care professional (specialist physician, dietitian, and psychologist) contacts.	Minimal and maximal costs per contact reported by the patients multiplied by the reported number of health care professional (specialist physician, dietitian, and psychologist) contacts.
Medications	The public price of each drug based on the exchange rates for the year 2011 (Lebanon National Drug Index, 2011; http://www.moph.gov.lb/Drugs/Documents/LNDI-2011.pdf).	N/A
Hospitalization	The average cost per day reported by the patients (US$189.25) multiplied by the reported number of days of hospitalization.	Minimal (US$22.70) and maximal (US$702.19) costs per day reported by the patients multiplied by the reported number of days of hospitalization.
Professional home care	The average cost per hour reported by the patients (US$24.45) multiplied by the reported number of hours of professional home care.	Minimal (US$10.13) and maximal costs (US$52.66) per hour reported by the patients multiplied by the reported number of hours of professional home care.
Costs to patient and family		
Informal care	The cost per 1 hour of informal care was calculated based on the minimum wage for the year 2011 in Lebanon (US$1.67) [Cost = minimum wage (US$349.34) ÷ the number of monthly work hours for the private sector (n. hours = 208), Ministry of Labor, 2008]. This cost was multiplied by the reported number of hours, where the patients needed help from family or friends.	N/A
	For patients who reported coming to the HD unit with a family member, relative or friend, additional productivity losses were estimated to be 1 hour per session (half an hour for transportation to and from the HD unit, respectively) with the same cost per hour.	
	For patients who reported that a family member, relative or friend accompanied them during the HD sessions, additional productivity losses were estimated to be 5 hours per session (1 hour for transportation as mentioned above, and 4 hours, which is the average time needed for of the HD session) with the same cost per hour.	

Resource	Valuation	
	Base-case analysis	**Sensitivity analysis**
Productivity losses	The human capital approach was used. For patients aged less than 64* and who are currently employed [Cost= the average salary in Lebanon (US$507.79) ÷ the number of monthly work hours for the private sector (n. hours = 208), CAS, 2009]. This cost was multiplied by the number of hours where the patient was unable to go to work (number of days reported by the patient multiplied by 8).	N/A
	For patients aged above 64 (complete) and who are currently employed: the same calculation was conducted, as above.	
	For patients aged less than 64 (complete) and who are currently unemployed: the same calculation was conducted, as above.	
	For patients aged above 64 (complete) and who are currently unemployed: the minimum wage was divided by the number of monthly work hours, and was then multiplied by the estimated reported number of hours, where the patients was not being able to perform daily activities (number of days reported by the patient multiplied by 4; assuming that the daily living activities equal the effort needed for a part-time job).	
Costs in other sectors		
Travel	For patients who reported coming to the HD unit by their own cars, or with a family member, relative or friend: an estimated cost of US$2.79 was applied to the trip from home to the HD unit and vice versa. This amount was considered as suitable to cover the average fuel consumption fees within the same area for 1 trip. It was estimated based on the fact that HD patients are usually assigned into a unit that is close (or within) their living area. This amount was multiplied by 2 to account for the trip back home or to work, and by the number of HD sessions per 6 months.	N/A
	For patients who reported coming to the HD unit by taxi: the 6-months transportation fees were calculated based on the reported fees per session incurred by the patients multiplied by the number of HD sessions per 6 months.	

*Retirement age in Lebanon is at 64. *HD: hemodialysis, N/A: not applicable*

CHAPTER 4

Effect of stage-based education provided by dedicated dietitians on hyperphosphataemic haemodialysis patients: results from the Nutrition Education for Management of Osteodystrophy randomised controlled trial

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ABSTRACT

Background: The Nutrition Education for Management of Osteodystrophy trial showed that stage-based nutrition education by dedicated dietitians surpasses existing practices in Lebanon with respect to lowering serum phosphorus among general haemodialysis patients. The present study explores the effect of nutrition education specifically on hyperphosphataemic patients from this trial.

Methodology: Hyperphosphataemic haemodialysis patients were allocated to a dedicated dietitian (DD), a trained hospital dietitian (THD) and existing practice (EP) protocols. From time-point (t)-0 till t-1 (6 months) the DD group (n=47) received 15 min of biweekly nutrition education by dedicated dietitians trained on renal nutrition; the THD group (n=89) received the usual care from trained hospital dietitians; and the EP group (n=42) received the usual care from untrained hospital dietitians. Patients were followed-up from t-1 till t-2 (6 months). Analyses used two-way repeated measures analysis of variance and Cohen's effect sizes (d).

Results: At t-1, phosphataemia significantly decreased in all groups (DD:-0.27mmol L^{-1}; EP:-0.15mmol L^{-1}; THD:-0.12mmol L^{-1}; $p<0.05$); the DD protocol had the greatest effect relative to EP (d=-0.35) and THD (d=-0.50). Only the DD group showed more readiness to adhere to a low phosphorus diet at t-1; although at t-2, this regressed to baseline levels. The malnutrition inflammation score remained stable only in the DD group, whereas the EP and THD groups exhibited a significant increase (DD: 6.74, 6.97 and 7.91; EP: 5.82, 8.69 and 8.13; THD: 5.33, 7.92 and 9.42, at t-0, t-1 and t-2, respectively).

Conclusion: The results of the present study suggest that the DD protocol decreases serum phosphorus compared to EP and THD, at the same as maintaining the nutritional status of hyperphosphataemic haemodialysis patients. Assessing the cost-effectiveness of the DD protocol is recommended.

KEYWORDS

Dietitians; haemodialysis; hyperphosphatemia; patient education.

INTRODUCTION

Hyperphosphataemia is consistently and independently associated with increased cardiovascular and all-cause morbidity and mortality in haemodialysis patients [1–7]. To manage this, patients must adhere to haemodialysis sessions, complex medication regimens and dietary phosphorus restriction [8,9]. However, adherence to a low phosphorus diet is found to be the poorest among all dietary restrictions [10] and almost half of haemodialysis patients have a serum phosphorus level higher than the recommended level of 1.78 mmol L^{-1} [8,11]. Hyperphosphataemia is the most common mineral abnormality among haemodialysis patients in developed and developing countries. It is even present among patients receiving optimal medical care [12,13].

Hyperphosphataemia management is a true challenge in modern nephrology, especially because phosphorus restriction often poses the risk of reducing protein intake, precipitating malnutrition, wasting and poor survival [14]. Consistent expert dietary education and regular follow-up are needed to help haemodialysis patients sustain a low phosphorus intake, subsequently normal phosphataemia, at the same time as maintaining a good nutritional status [8,9,15].

Nutrition education, especially when utilizing cognitive or behavioural components improves phosphorus control among haemodialysis patients [16–19]. Nevertheless, stronger evidence is needed to better identify optimal frequency and approaches of dietetic education to ensure long-term dietary phosphorus management without compromising the nutritional status of patients [19,20].

The Nutrition Education for Management of Osteodystrophy (NEMO) trial [21] assessed the effect of a 2 hours per month stage-based nutrition education using the transtheoretical model of behavioural change on serum phosphorus control in the general haemodialysis population. NEMO reported statistically significant improved phosphataemia management, increased adherence to (and knowledge of) a low phosphorus diet, and decreased deterioration in patients' quality of life and nutritional status [22,23]. However, the effect of this intervention specifically on patients with hyperphosphataemia was not explored. This subpopulation has higher risks of morbidity and mortality as a result of hyperphosphataemia, among whom achieving normal phosphataemia is recommended. In the present study, we aimed to assess, via a pre-specified analysis of the NEMO trial, the effectiveness of intensive stage-based nutrition education provided by dedicated dietitians on hyperphosphataemia management among hyperphosphataemic haemodialysis patients and to compare this with the existing practices in Lebanon.

MATERIALS AND METHODS

We used data from the NEMO trial, a multicentre randomised controlled trial conducted in 12 hospital-based haemodialysis units in Lebanon [21].

Participants

For the NEMO trial, eligible patients were those treated in recruited haemodialysis units, comprising Lebanese, adults (≥18 years), free of cancer, infection with the human immunodeficiency virus and hepatitis, not having undergone major surgery in the past 3 months, on haemodialysis for at least 6 months, able to understand the procedure of the study, able to communicate verbally or through writing, and willing to participate in the study. Informed consent was obtained from all participants prior to the start of the study.

For the current analysis, patients had to meet the above-mentioned criteria; moreover, they had to be hyperphosphataemic. Hyperphosphataemia was defined as a mean serum phosphorus for the 6 months prior to the beginning of the NEMO trial >1.78 mmol L^{-1} [Kidney Disease Outcomes Quality Initiative guidelines [8]]. Eligibility criteria were confirmed through a review of the patient medical charts.

Design

A detailed description design is provided in Karavetian et al. [21]. In brief, participants were followed for 12 months, and measures were collected at 3 time-points (t): t-0 (beginning of month 1: July, 2011), t-1 (end of month 6) and t-2 (end of month 12: June 2012). Twelve hospital-based haemodialysis units were randomly recruited to the NEMO trial from the official list of hospital-based haemodialysis units in Lebanon. They were simple randomly assigned to cluster A (six units) and cluster B (six units) using EXCEL (Microsoft Corp., Redmond, WA, USA). Cluster A patients were then assigned according to their haemodialysis shifts into two protocols: Dedicated Dietitian (DD) and Existing Practice (EP). Cluster B patients were assigned to the Trained Hospital Dietitian (THD) protocol.

From t-0 till t-1, the 3 groups received the following interventions:

- DD group: dietitians in this group received a formal training on renal dietetics [24] and were dedicated only to haemodialysis units. They provided the patients with 15-min biweekly individualized educational sessions (seven sessions per month) considering the patient stage of behavioural change towards a low phosphorus diet, using a renal-oriented culturally-validated educational tool based on the transtheoretical model of behavioural change [21,22]. DD also provided the patients with a 1-monthly reinforcement session, where the phosphataemia result was discussed and a new target was set for the coming month using motivational interviewing. The stage-based nutrition education was conveyed during the haemodialysis sessions because this timing is optimal for educating haemodialysis patients [16]. In these units, the existing practice was not compromised and hospital dietitians continued providing their standard care.

- EP group: patients received the usual care by their hospital dietitians, who did not receive any additional training on renal dietetics. This group reflected the situation in Lebanon, where hospital dietitians have limited knowledge on renal dietetics and where care of haemodialysis patients constitutes a small proportion of their hospital responsibilities [25]. In this group, dietetic consults were performed only upon nephrologists' requests.
- THD group: patients received usual care by their hospital dietitians who were educated on renal dietetics to an equal extent as the dietitians in the DD group, although they were not dedicated to haemodialysis patients. Accordingly, no minimal dietitian-patient time was set for this group and dietitians were left to continue providing their usual care.

A follow-up period, with no intervention in all groups, followed from t-1 until t-2.

Throughout the study, hyperphosphataemic patients in the three groups underwent the same interventions as their fellow normo-or hypophosphataemic patients.

The NEMO trial obtained ethical approval from the institutional review boards of participating institutions.

OUTCOME MEASURES AND ASSESSMENT TOOLS

Consistent with the NEMO trial [21], outcome measures included serum phosphorus (mmol L^{-1}), dietary phosphorus (mg day^{-1}) and phosphorus-to-protein ratio (mg g day^{-1}) intake, stage of behavioural change towards a low phosphorus diet and the malnutrition inflammation score.

Serum phosphorus (mmol L^{-1}) comprised the primary outcome. This was retrieved from the medical charts of patients. The 6-month mean values were calculated at the three time-points.

Phosphorus (mg day^{-1}) and phosphorus-to-protein ratio (mg g day^{-1}) intakes were estimated by a 3-monthly 24-h recalls, analysed using the USDA database [26]. The 6-month mean values were calculated at the three time-points.

Stage of behavioural change towards a low phosphorus diet was assessed on a monthly basis via a decisional tree based on the transtheoretical model of behavioural change [27], with the components being modified to address phosphataemia and a low phosphorus diet. Patients were assigned to each stage according to their scores (1, Precontemplation; 2, Contemplation; 3, Preparation; 4, Action; 5, Maintenance). Higher scores indicated a greater readiness to adhere to a low phosphorus diet. The 6-month mean values were calculated at the three time-points.

The nutritional and inflammatory status was assessed via the malnutrition inflammation score. This is a renal-tailored tool, associated with measures of nutrition, atherosclerosis, inflammation, anaemia, quality of life, hospitalization and mortality among haemodialysis patients. It is the gold standard for examining other scoring systems for the malnutrition-inflammation complex syndrome [28–31]. The malnutrition inflammation score has 10 components, with four levels of severity ranging from 0 (normal) to 3 (severely abnormal). The total score ranges from 0 to 30, with a higher score reflecting more severe degrees of malnutrition and inflammation. The biochemical components of the score were collected from the medical charts of patients. The malnutrition inflammation score was calculated at the three time-points.

Outcomes were collected by trained research dietitians using prepiloted standardized forms.

STATISTICAL ANALYSIS

Data from participants who failed to complete the study because they were transferred, received a transplant, died, or withdrew, were not included in the analysis. Analyses were conducted using the SPSS, version 21 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used for sample characteristics. Chi square and Fisher's Exact tests were used to assess between-group baseline differences of categorical variables. One-way analysis of variance (ANOVA) and the Kruskal-Wallis test followed by a Mann-Whitney test and Bonferroni correction were used to assess between-group baseline differences of continuous variables. The effects of the three protocols (DD versus EP versus THD) on study outcomes and their interactions over time (t-0 versus t-1 versus t-2) were analysed using two-way repeated measures ANOVA, with protocol and time being the between- and within-group factors, respectively. Accordingly, the effect of the intervention was assessed within each group at the three time-points, as well as between the three groups at each time-point. Where a statistically significant effect was found, post-hoc Bonferroni comparisons were undertaken. Cohen's d effect size measures were calculated for serum phosphorus to examine the magnitude of the effect of each protocol at t-1 [32]. $d<|0.2|$ reflected no effect, $|0.2|$ was considered low, $|0.5|$ medium, and $|0.8|$ large [33]. A negative d represented improvement because phosphataemia is a negative-oriented outcome (higher values indicate deterioration) [34]. $P<0.05$ was considered statistically significant.

RESULTS

Twelve hospital-based haemodialysis units were included in the present study. Of the 570 patients who met the inclusion criteria of the NEMO trial, 235 patients were also hyperphosphataemic (DD: 65; EP: 57; THD: 113). Of these, 178 completed the study (DD: 47; EP: 42; THD: 89) and were included in the current analysis. Attrition was almost similar in the three groups (DD: 27.7%, EP: 26.3%; THD: 21.2%) (Figure 1).

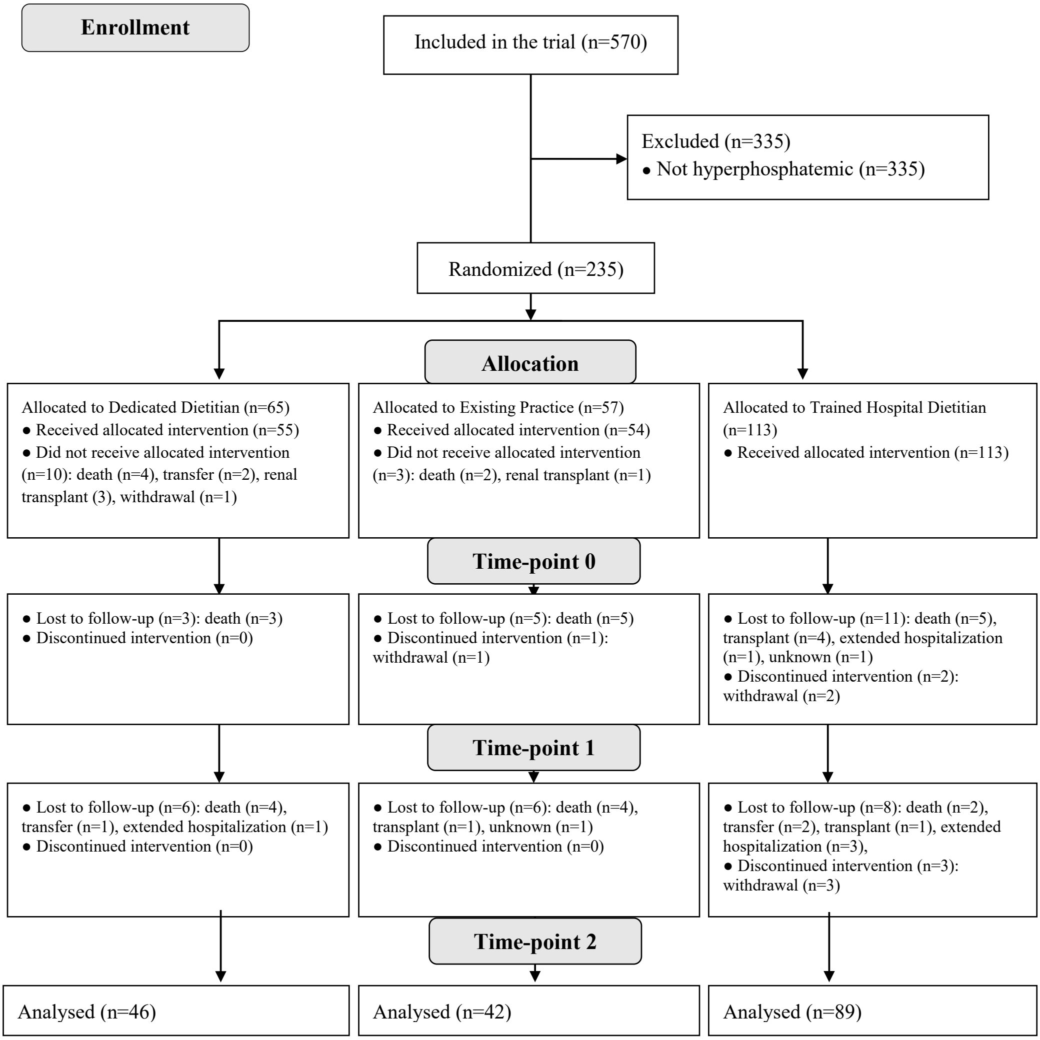

Figure 1. *Flow Diagram of the Trial.*

PARTICIPANTS' CHARACTERISTICS

At baseline, DD, EP and THD patients were generally similar in terms of sociodemographic and clinical characteristics (Table 1). Participants were relatively young (mean age: 56.5 years), more than half were males (58.4%), and one-third reached high school (21.9%) and university (11.2%) education. Approximately one-third (35.4%) were employed and the majority (77.5%) were married. One-third (30.3%) had diabetes, two-thirds (64.0%) were hypertensive and 14.6% had concomitant cardiovascular diseases. The patients were on haemodialysis for 51.3 months, on average, with a mean of 10.4 h of treatment per week. Patients in the EP group spent less time on treatment than those in the DD and THD groups (9.1 h versus 10.7 and 10.8 h, respectively). Mean parathormone levels were normal (447.0 ng L^{-1}). On average, calcium-phosphorus byproduct was higher than the recommended level (4.76 $mmol^2$ L^{-2}) (63). Mean body mass index was 25.3 kg m^{-2}; patients in the DD group had a greater body mass index than those of the THD group (26.8 vs. 24.2 kg m^{-2}).

Table 1. *Participants' Characteristics [% or mean (SD)] (n=178)*

	Dedicated Dietitian (n=47)	**Existing Practice (n=42)**	**Trained Hospital Dietitian (n=89)**
Male (%)	44.7	61.9	64.0
Social Status (%)			
Single	23.4	9.5	18.0
Married	68.1	85.7	78.7
Other	8.5	4.8	3.4
Employed (%)	34.0	26.2	40.4
Educational Level (%)			
Illiterate	19.1	14.3	18.0
Read & Write	17.0	14.3	14.6
Elementary	36.2	23.8	38.2
High school	21.3	31.0	18.0
University	6.4	16.7	11.2
Co-morbidities (%)			
Diabetes	43.2	26.2	27.0
Hypertension	73.3	61.9	61.8
Cardiovascular diseases[a]	27.3	9.5	11.2
Other[b]	39.3	22.7	9.8
Age (years) (mean (SD))	54.36 (16.54)	57.71 (13.86)	57.03 (15.91)
Vintage (months) (mean (SD))	50.78 (46.92)	48.08 (46.50)	53.12 (53.27)
Hemodialysis time (h $week^{-1}$) (mean (SD))	10.77 (2.71)[c]	9.10 (2.98)[cd]	10.89 (1.84)[d]
Parathormone (ng L^{-1}) (mean (SD))	417.95 (445.18)	412.73 (348.21)	474.07 (399.75)
Calcium-Phosphorus Byproduct ($mmol^2$ L^{-2}) (mean (SD))	4.75 (0.93)	4.68 (0.70)	4.80 (0.83)
Body Mass Index (kg m^{-2}) (mean (SD))	26.86 (5.53)[c]	26.16 (4.98)	24.24 (3.84)[c]

[a]$p<0.05$ indicates a difference between-groups based on a chi-squared test, [b]$p<0.05$ indicates a difference between-groups based on Fisher's exact Test, [c,d]$p<0.05$ indicates a difference between-groups based on a Kruskal-Wallis test followed by a Mann-Whitney test and Bonferroni correction.
Table 2 summarizes changes in study outcomes of patients who finished the 12-month trial.

Table 2. *Study Outcomes per Protocol at the Three Time-Points [mean (SD)] (n=178)*

		Dedicated Dietitian (n=47)	Existing Practice (n=42)	Trained Hospital Dietitian (n=89)
Serum Phosphorus (mmol L^{-1})	**t-0**	2.20 (0.35)^{ab}	2.18 (0.33)^{a}	2.15 (0.30)^{a}
	t-1	1.92 (0.41)^{a}	2.02 (0.47)^{ab}	2.03 (0.39)^{a}
	t-2	1.96 (0.52)^{*,b}	2.22 (0.58)^{*,b}	2.03 (0.42)
Malnutrition-Inflammation Score	**t-0**	6.74 (3.22)	5.82 (2.88)^{ab}	5.33 (3.72)^{ab}
	t-1	6.97 (3.59)	8.69 (3.85)^{a}	7.92 (3.33)^{ac}
	t-2	7.91 (3.86)	8.13 (3.41)^{b}	9.42 (4.03)^{bc}
Stage of Behavioural Change	**t-0**	2.72 (1.35)^{a}	2.64 (1.17)	2.92 (1.25)^{a}
	t-1	4.11 (0.53)^{*,**,a}	2.67 (1.09)*	2.71 (1.12)^{**,b}
	t-2	2.56 (1.04)	2.73 (0.93)	2.33 (1.19)^{ab}
Phosphorus Intake (mg day^{-1})	**t-0**	814.98 (396.60)^{ab}	985.80 (359.81)^{*,ab}	762.04 (382.49)*
	t-1	667.70 (233.64)^{a}	812.18 (310.76)^{ac}	783.26 (276.78)^{a}
	t-2	591.62 (254.74)^{b}	548.29 (225.44)^{*,bc}	701.16 (310.10)^{*,a}
Phosphorus-to-Protein Ratio (mg g day^{-1})	**t-0**	15.60 (4.61)	16.73 (3.98)	14.81 (4.32)^{a}
	t-1	15.78 (4.59)	15.18 (4.08)	15.46 (3.93)
	t-2	16.33 (2.58)	15.84 (1.51)	16.05 (2.15)^{a}

t: time-point.
^{abc} Differences across columns indicate significant differences (p<0.05) within each group at t-0 versus t-1 versus t-2, *,** differences across in rows indicate significant differences (p<0.05) between the groups (dedicated dietitian versus existing practice versus trained hospital dietitian) at each of the three time-points, based on two-way repeated measures analysis of variance with post-hoc comparisons using Bonferroni correction.

SERUM PHOSPHORUS (MMOL L^{-1})

At baseline (t-0), serum phosphorus was similar between the three groups. Following the intervention (t-1), phosphataemia significantly dropped in all groups, with no differences between them. The greatest decrease was noted among DD patients (0.27 mmol L^{-1} vs. 0.15 mmol L^{-1} and 0.12 mmol L^{-1} in the EP and THD groups, respectively). DD protocol had a medium greater effect than THD protocol (d=-0.50) and low greater effect relative to EP protocol (d=-0.35). THD and EP protocols had no superiority over each other (d=-0.12). At 6-month post-intervention (t-2), serum phosphorus remained significantly lower than baseline levels only in the DD group, whereas it increased to baseline levels in the EP and THD groups. At t-2, patients in the DD group had a significantly lower phosphataemia than those in the EP group.

MALNUTRITION INFLAMMATION SCORE

At baseline, the malnutrition inflammation score was similar between the three groups. It remained stable only in the DD group throughout the study. By contrast, the other groups exhibited a significant increase in their mean score (EP: 5.82, 8.69 and 8.13; THD: 5.33, 7.92 and 9.42 at t-0, t-1 and t-2, respectively), indicating a worsened nutritional status over time.

STAGE OF BEHAVIOURAL CHANGE

At t-0, patients were, on average, in the pre-action stage of behavioural change towards low phosphorus diet, without significant differences between the three groups. At t-1, only patients in the DD group progressed to the action stage and were significantly more ready to adhere to a low phosphorus diet than patients in the EP and THD groups who stagnated in the pre-action stage. At t-2, DD patients regressed to baseline levels. Patients in the THD group exhibited a continuous significant regression in their readiness to adhere to a low phosphorus diet throughout study period. At the end of the intervention, all groups returned to the pre-action stage.

PHOSPHORUS INTAKE (MG DAY^{-1})

From t-0 till t-1, reported phosphorus intake significantly dropped in the DD and EP groups. Reported phosphorus intake further decreased in all groups at t-2.

PHOSPHORUS-TO-PROTEIN RATIO (MG G^{-1} DAY^{-1})

No changes between- or within-group were noted throughout the study, except in the THD group who showed a significant increase in dietary phosphorus-to-protein ratio between t-0 and t-1.

DISCUSSION

The present study explored the effect of nutrition education based on the transtheoretical model of behavioural change and provided by DD on the outcomes of hyperphosphataemic haemodialysis patients, who as a result of hyperphosphataemia, are at increased risks of morbidity and mortality; and for whom the intervention aiming to decrease serum phosphorus is appropriately targeted. The participants shared characteristics common to hyperphosphataemic haemodialysis patients [35–41]; they were relatively young, predominantly males and literate.

Educating hyperphosphataemic haemodialysis patients based on the transtheoretical model of behavioural change by a dedicated competent dietitian for 30 min per week, during 6 months, significantly improved their readiness to adhere to a low phosphorus diet and decreased their phosphataemia without compromising their nutritional status. This was conducted without the need for additional resources, except ensuring adequate dietitian education and dietitian-patient time. The DD protocol was superior to the other protocols: EP representing the existing practice in Lebanon (i.e. no specialisation for dietitians in renal dietetics and no imposed dietitian-patient time), and THD representing a viable alternative, which is ensuring dietitian education without imposing a minimum dietitian-patient time.

The results of this analysis are in line with the findings of the NEMO trial [22,23]. Following the intervention, a significant drop in phosphataemia was noted among patients in the three groups. The greatest effect was noted in the DD group. The finding of this group might be explained by the effect of intensive dietitian-led education, resulting in the enhanced adherence of patients to a low phosphorus diet, as exhibited by their improved stage of behavioural change. Strong evidence supports the beneficial effect of dietitian involvement in haemodialysis care, especially in phosphorus management [19]. In the DD group, the dietitians monitored the progress of each patient and had adequate time to provide individualized evidence-based education. Implementing practice guidelines not only relies on their scientific validity, but also on their usability by clinicians [42], where insufficient time is a crucial barrier [43]. Even the most qualified and organized dietitian is unable to provide quality care when time allocation with patients is inadequate [44]. Insufficient time to provide care for haemodialysis patients was commonly noted among Lebanese hospital dietitians [25]. Besides time factor, DD intervention comprised aspects not widespread among Lebanese hospital dietitians [25]: the educational material was culturally-specific and the dietitians were extensively trained on renal dietetics.

Possible factors might explain the significant drop in phosphataemia post-intervention in the other groups. As reported in Karavetian et al. [22], the mild improvement in the THD group, might be attributed to the fact that dietitians in this group upgraded their educational methods and increased the frequency of consultations after receiving the training. However, the intensity of the education remained suboptimal, resulting in a lower improvement in phosphataemia. This explanation is supported by our data (M. Karavetian) showing that dietitians in the THD group visited the patients at best once monthly. This was expected considering the schedule overload of these dietitians [25]. As for the EP group, contamination of information through patients and nurses took place [22]. Patients in this group were subject to passive education because educational posters and material were hung on the dialysis units' walls during the intervention period and DD patients who changed their dialysis shifts might have shared the new knowledge with their peers who were in the EP group. Moreover, nurses transferred the educational material from the DD to the EP group.

The decrease in serum phosphorus should not be regarded as sole outcome of this intervention and should be interpreted in the light of other findings, notably the nutritional status. While all patients had a higher malnutrition inflammation score at the end of the study (denoting a worsened nutritional status), this increase was significant only in the EP and THD groups and not in the DD group. This reinforces that only intensive, timely and individualized education by competent dietitians resulted in careful and effective care (decreased phosphataemia, without compromising the patients' nutritional status) [8,9,15]. This is a key finding for clinical practice and policy makers because worsened nutritional status of haemodialysis patients is associated with increased morbidity and mortality and higher healthcare costs [14,45].

The intensive stage-based nutrition education created a momentum for improving patient adherence to a low phosphorus diet, through enhancing their self-management skills and collaborating involvement in their disease management. Nevertheless, this progress was lost when the intervention resolved. Relapse and regression are natural steps within the behavioural change cycle [46]. Evidence suggests that the effect of an intervention (if not provided continuously) might fade over time [22,47]. This might translate into an increase in phosphataemia over the long term and relapse towards baseline values.

Discussing the results of dietary phosphorus and phosphorus-to-protein ratio is challenging. The 24-h recall is often biased in haemodialysis patients since it relies on the patient's ability to remember and accurately report consumed foods. The 24-h recall often underestimates actual intake, even when conducted by a trained interviewer, and can generate a great variability in the mean daily nutrient intake [48]. A lack of data pertaining to potential confounders is another limitation for the present study: hospitals did not routinely provide information on dialysis adequacy (Kt v^{-1}, urea reduction ratio) and medication prescription (vitamin D, phosphate binders). However, random allocation of groups would most likely result in a similar distribution of hospitals based on quality of medical care. The positive results noted in the DD group might not be only due to the adherence to a low phosphorus diet but also greater adherence to phosphate binders because some of the educational sessions emphasized their importance. The design of the present study did not allow this issue to be assessed because the prescription of phosphate binders within Lebanese haemodialysis units is within the sole authority of nephrologists. This issue remains to be explored by future studies. The final major limitation to the present study is the contamination of information between the DD and EP groups, and the potential underestimation of the true effectiveness of the DD protocol. Opting for this design was informed by a study by Griva et al. [49] among haemodialysis patients, who argued that allocation of participants based on their shift would limit cross-contamination of information between groups. However, we encountered an opposite effect in our trial. This learning experience should inform the design of future studies among haemodialysis patients, by alerting researchers that the prevention of contamination through allocation of participants based on their dialysis shift is not always possible, and resorting to running the trial in different units might be a more suitable alternative in this patient-population. Stage-based nutrition education provided by trained dietitians on the basis of 30 minutes per week is an effective approach for improving hyperphpsphataemic haemodialysis patients' adherence to low phosphorus diet and decreasing their serum phosphorus without compromising their nutritional status. This protocol is superior to the existing practice (EP) in Lebanon and to the other possible alternative (THD). The assessment of the cost-effectiveness of the DD protocol for reimbursement reasons is recommended as a next step, and its implementation in Lebanese haemodialysis units should be advocated, if it is shown to be cost-effective. This assessment is needed to better inform the integration of this model in routine practice, especially in the light of the high cost and the nonconclusive evidence behind the cost-effectiveness of other phosphorus-lowering interventions in this population (i.e. non-calcium-based phosphate binders) [50].

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None.

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CHAPTER 5

COST-EFFECTIVENESS OF DEDICATED DIETITIANS FOR HYPERPHOSPHATEMIA MANAGEMENT AMONG HEMODIALYSIS PATIENTS IN LEBANON: RESULTS FROM THE NUTRITION EDUCATION FOR MANAGEMENT OF OSTEODYSTROPHY TRIAL

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[Submitted]

ABSTRACT

Objective: To assess the cost-effectiveness of nutrition education by dedicated dietitians (DD) for hyperphosphatemia management among hemodialysis patients.

Design: Trial-based economic evaluation.

Setting: 12 Lebanese hospital-based units.

Subjects: 545 prevalent patients, allocated by cluster randomization to DD, trained hospital dietitian (THD) and existing practice (EP) groups.

Intervention: Phase I (6 months): DD group (n=116) received intensive education by DD trained on renal nutrition; THD (n=299) received usual care from trained hospital dietitians; EP (n=130) received usual care from untrained hospital dietitians. Patients were followed-up during Phase II (6 months).

Main outcome measures: Resources use, societal costs, serum phosphorus, quality-adjusted life-years (QALYs).

Results: At baseline, EP had the lowest weekly hemodialysis time and DD had the highest mean serum phosphorus and malnutrition-inflammation score. The additional costs of the intervention were low compared with the societal costs (DD: \$76.7, \$21,007.7; EP \$4.6, \$18,675.4; THD: \$17.4, \$20,078.6, respectively). Between Phases I and II, DD showed the greatest decline in services use and the highest mean decrease in societal costs (DD: -\$2,364.0; EP: -\$1,727.7; THD: -\$1,105.7). At endline, DD experienced the greatest mean decrease in adjusted serum phosphorus (DD: -0.32; EP: +0.16; THD: +0.04 mg/dL), no difference in QALY, and the highest societal costs. DD protocol had a cost-effectiveness ratio of \$7,853.6 per 1 mg decrease in phosphorus, compared with EP; and was dominated by THD. Regarding QALY, DD was dominated by EP and THD. The results were sensitive to changes in key outcomes.

Conclusion: DD protocol yielded the greatest effectiveness and decrease in costs, but did not affect QALY. Regarding serum phosphorus, it was likely to be cost-effective compared with EP but had a low probability of being cost-effective compared with THD. Regarding QALY, DD was not likely to be cost-effective. Assessing the long-term cost-effectiveness of DD protocol, on similar groups, is recommended.

KEYWORDS

Cost-effectiveness analysis; dietitians; patient education; hyperphosphatemia; hemodialysis.

INTRODUCTION

Elevated serum phosphorus is a serious consequence of the chronic kidney disease. It is associated with increased patient morbidity [1], mortality [2–5], and high healthcare costs [6]. International clinical practice guidelines recommend "normalizing" serum phosphorus of hemodialysis patients through dialysis, phosphate-binding medications, and low phosphorus diet [7,8]. However, more than a decade after the first guidelines were issued, hyperphosphatemia remains a common condition among renal patients, especially those treated with hemodialysis, with nearly 1 in 2 patients being hyperphosphatemic [9,10].

Economic evaluations are a useful tool to identify the economic value of an intervention and guide decision making. Up-till-now, in hyperphosphatemia management, efforts were focused on one intervention: phosphate binders [11] and despite the mounting evidence on the clinical effectiveness of dietary education [12], the cost-effectiveness of this intervention has not been addressed [11].

The most recent local evidence on the effectiveness of dietetic interventions for hyperphosphatemia management among prevalent hemodialysis patients emanate from the Nutrition Education for Management of Osteodystrophy (NEMO) trial [13]. Results from the NEMO trial showed that intensive education by DD was superior to the other protocols in reducing serum phosphorus, without compromising the nutritional status of the patients [14–16]. Assessing the value for money of DD would be very important for helping decision makers efficiently allocate scarce resources devoted to hemodialysis patients.

The aim of this study was therefore to conduct an economic evaluation (including a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA)), from the societal perspective of DD vs. EP and THD interventions in hemodialysis patients in Lebanon.

METHODS

We used individual patient-level data from the NEMO trial to perform the CEA and CUA and followed international guidelines for the analysis and reporting of economic evaluations [17,18]. A societal perspective was used, with a time horizon of 1 year.

TRIAL

Design

The design, methods and clinical results of the NEMO trial are detailed elsewhere [13–16]. The NEMO trial was conducted in Lebanon and compared three protocols of nutrition education for hyperphosphatemia management among hemodialysis patients. In brief, 12 hospital-based hemodialysis units (n=570) were randomly assigned to cluster A (6 units; n=271) and cluster B (6 units; n=299). Cluster A patients were then equally assigned according to their hemodialysis shifts into 2 protocols: DD (n=133) and EP (n=138); cluster B patients were assigned to THD protocol. Participants were followed for 12 months, and measures were collected at 3 time-points: t-0 (beginning of month 1), t-1 (end of month 6) and t-2 (end of month 12). The NEMO trial received ethical approval from the ethical committees of participating hospital-based hemodialysis units, and was conducted according to the Declaration of Helsinki.

Subjects

Consenting patients, adult, receiving dialysis for at least 6 months, free of cancer, infection with human immunodeficiency virus and hepatitis C were considered.

Interventions

Phase I (t-0 till t-1: 6 months): DD group received intensive nutrition education during hemodialysis sessions by trained dietitians dedicated to hemodialysis units, on a basis of 2 hours per month. The existing practice was not compromised in these units, and hospital dietitians were left to provide their usual care; EP group received usual care by their hospital dietitians, where patients' consults are upon the nephrologists' requests (this group represented the existing practice in Lebanon, where no dietitians are dedicated to hemodialysis patients); and THD group received usual care by their hospital dietitians who were equally trained on renal nutrition as the dedicated dietitians, but were not devoted to hemodialysis patients in particular (this group represented an alternative to having a dedicated dietitian; whereby hospital dietitian's education is ensured, but dietitian-to-patient time is not set).

Phase II (t-1 till t-2: 6 months) was a follow-up period.

ECONOMIC EVALUATION

Outcomes

The outcome of the CEA was serum phosphorus, and that of the CUA was quality-adjusted life-year (QALY). QALY incorporates the quality of a health state (quality-of-life: QoL) with the duration of survival (life-years: LYs) using a multiplicative formula. It is the preferred and most common outcome in economic evaluation [19]. QoL was measured with the Short Form (SF)-36 questionnaire, assessing the 2 dimensions of physical and mental health over the past 30 days [20]. Patients completed the validated culturally-specific pilot-tested version of the SF-36 [13,21] at t-0, t-1 and t-2. Serum phosphorus was retrieved from the patients' medical charts, and its 6-month mean values were calculated at the 3 time-points.

Costs

Cost data were collected at t-1 and t-2, following the 3 steps of costs identification, measurements and valuation, as detailed in Rizk et al. [22]. Costs identification: included costs were categorized as (1) healthcare sector costs (cost of the dietetic intervention, costs associated with hemodialysis, emergency hemodialysis, healthcare professional consultation, hospitalization, medications, and integrated home care); (2) costs to patient and family (caregiver costs and productivity losses); and (3) costs in other sectors (travel costs) [17]. Costs measurement: using a pilot-tested resource utilization questionnaire (Appendix S1) adapted to Lebanese hemodialysis patients. Costs valuation: the costs were gathered and calculated in Lebanese pounds (LBP), converted to US$ (1 US$= 1,507.5 L.L.; year of reference: 2011) [23] and uprated to 2015US$ using Consumer Price Indices (Index, 2010=100) [24]. A macro-costing valuation was applied, whereby composite intermediate resources were identified and measured. The mean reported costs incurred by patients were used to value the costs of emergency hemodialysis, consultations with healthcare professionals, hospitalizations, and professional care. The costs of drugs were derived from the Lebanese National Drug Index [25]. Valuation of informal care was based on the proxy good method [26] and valuation of productivity losses was based on the human capital approach [27]. Costing of the intervention in each group is detailed in Appendix S2. The reported quantity/frequency of use of each service was multiplied by its respective mean cost to obtain the total costs. Discounting was not applied, as the analysis was limited to 1 year.

Preparation of data

Serum phosphorus was adjusted for baseline differences between the three groups, following a regression method controlling for baseline serum phosphorus, age, gender, weekly hemodialysis time and malnutrition-inflammation score (MIS), as detailed by van Mastrigt et al. [28]. For the base-case CEA, missing values of patients who withdrew during Phase I were replaced by their baseline value minus half of the difference in serum phosphorus between t-0 and t-1 of participants from the same unit and study group (peers), assuming that the patients attrited at mid-point of the phase and that evolution of serum phosphorus was linear. For Phase II, missing values were replaced by the patients' values at t-1 minus the difference in serum phosphorus between t-1 and t-2 of their peers.

For the CUA, SF-36 QoL data were converted to utility [29]. Mean utility between t-0 and t-1; and between t-1 and t-2 were retained for Phase I and Phase II, respectively. Missing QoL data were imputed by last observation carried forward, when available, or by the mean of the peers. Regarding LYs, for each phase survived, patients were allocated 0.5 LYs. Patients not surviving the phase due to mortality or extended hospitalization were allocated 0.25 LYs, assuming that they withdrew at the mid-point of the study phase. The LYs of those who were transferred, got a transplant, or withdrawal were imputed by the mean of their peers. QALYs was the product of utility and LYs. Total QALYs were obtained by summing QALYs at each phase. As for the costs, the missing values of patients who survived the phase were imputed by the mean of their peers. For those who died or were extensively hospitalized, their values were imputed by half of the mean costs of their peers, for the same above-mentioned reasoning. Those who attrited for other reasons were attributed the mean costs of their peers in parallel to their LYs.

Analyses

Analyses were conducted using SPSS. Descriptive statistics were generated. Chi square and Student's T test were used to determine baseline between-group differences for categorical and continuous data, respectively. One-way ANOVA followed by Bonferroni Post Hoc were used to assess the between-group differences in costs at t-1 and t-2. $p<0.05$ was used for significance. To determine the cost-effectiveness and cost-utility of DD, incremental cost-effectiveness and cost-utility ratios (ICERs, ICURs) were calculated. The ICER/ICUR is a ratio that compares the additional costs and effects of the assessed intervention with the control. The cost-effectiveness and cost-utility of DD vs. EP/THD were calculated as the difference in mean costs (C) divided by the difference in mean effects (E) (serum phosphorus and QALY, respectively) at t-2:

DD vs. EP=$(C_{DD} - C_{EP})/(E_{DD} - E_{EP})$; DD vs. THD=$(C_{DD} - C_{THD})/(E_{DD} - E_{THD})$.

Sensitivity analyses

Three one-way sensitivity analyses were performed to test the robustness of the results of the base-case. The first analysis assessed the effects of excluding maintenance hemodialysis and transportation costs, following the reasoning of Grima et al. [30]. The second analysis examined the impact of imputation; and accordingly included complete cases only. The third analysis was carried out only on hyperphosphatemic patients (phosphorus >5.5mg/dL) at baseline, as they are at higher risks for morbi-mortality and are reported to have higher costs than normophosphatemic patients. In the final analysis, we used for the CEA, the mean unadjusted serum phosphorus difference between t-2 and t-0; and for the CUA, we used the adjusted QALYs (regression-based QALY adjustment), since QoL is associated with clinical outcomes among hemodialysis patients, including hospitalization and mortality [20,31].

Non-parametric bootstraps were conducted to assess the stochastic uncertainty in the data using the bootstrapping technique in Excel, where the original sample was re-sampled, resulting in 5000 simulated ICERs/ICURs per scenario. Cost-effectiveness/utility acceptability curves (CEACs/CUACs) were plotted using the probability estimates of DD's cost-effectiveness (compared with each of the other interventions) over a range of willingness-to-pay (WTP) thresholds. The latter were defined as the amount of money the society is willing to pay to gain one unit of effect. In Lebanon, the value the society is willing to pay to gain one QALY is not defined. Accordingly, we used several thresholds ranging from 3 times the Gross Domestic Product in Lebanon ($31,272.84)- threshold suggested by the World Health Organization [32,33] to £30,000 ($43,612.49)- explicit threshold adopted in the United Kingdom [34], and $50,000- implicit threshold adopted in the United States [35].

RESULTS

PATIENTS' CHARACTERISTICS

The flow diagram of the trial is detailed in Appendix S3. At baseline, the three groups were comparable with respect to sociodemographic characteristics, except for employment status. Weekly hemodialysis time was significantly lower in the EP group. DD group had the highest mean serum phosphorus, which was above the recommended range [7]. DD group had the highest mean MIS, denoting the worst malnutrition-inflammation status (Table 1).

Table 1. *Participants' characteristics (n=545)*

	DD (n=116)	**EP (n=130)**	**THD (n=299)**
Male (%)	66 (56.9)	72 (55.4)	182 (60.9)
Social Status (%)			
Single	26 (22.4)	18 (13.8)	44 (14.7)
Married	83 (71.6)	102 (78.5)	242 (80.9)
Other	7 (6.0)	10 (7.7)	13 (4.3)
Employed (%)*	38 (32.8)	24 (18.5)	99 (33.1)
Educational Level (%)			
Illiterate	23 (19.8)	28 (21.5)	79 (26.4)
Read & Write	17 (14.7)	22 (16.9)	33 (11.0)
Elementary	38 (32.8)	36 (27.7)	108 (36.1)
High school	24 (20.7)	24 (18.5)	43 (14.4)
University	14 (12.1)	20 (15.4)	36 (12.0)
Co-morbidities (%)			
Diabetes	39 (36.1)	50 (38.5)	99 (33.2)
Hypertension	77 (69.4)	83 (63.8)	203 (68.1)
Cardiovascular diseases	30 (27.8)	27 (20.8)	62 (20.9)
Other*	29 (40.3)	22 (25.6)	17 (16.3)
Age (years) (mean (SD))	57.56 (15.18)	59.96 (15.22)	60.51 (14.94)
Utility (mean (SD))	0.56 (0.06)	0.56 (0.06)	0.55 (0.06)
Vintage (months) (mean (SD))	61.02 (64.39)	46.94 (48.62)	57.30 (53.06)
HD time (hours/week) (mean (SD))	10.64 (2.49)‡	9.53 (2.77)‡§	11.14 (1.45)§
Sodium† (mEq/L) (mean (SD))	59.61 (2.41)	58.88 (4.71)‡	59.88 (0.64)‡
Potassium† (mEq/L) (mean (SD))	1.34 (0.22)	1.35 (0.22)	1.33 (0.20)
Phosphorus† (mg/dL) (mean (SD))	5.57 (1.52)‡	5.39 (1.49)	5.16 (1.44)‡
Calcium† (mg/dL) (mean (SD))	8.66 (0.80)‡	8.62 (0.97)	9.11 (1.57)‡
CaP† (mg^2/dL^2) (mean (SD))	48.37 (14.43)	46.65 (13.56)	47.11 (15.09)
PTH† (pg/mL) (mean (SD))	400.85 (457.61)	377.52 (360.64)	344.89 (338.50)
Albumin† (g/L) (mean (SD))	38.76 (3.77)	39.42 (4.28)	39.74 (4.36)
MIS (mean (SD))	7.30 (3.31)‡	6.55 (3.17)	6.07 (3.90)‡
BMI (Kg/m^2) (mean (SD))	25.10 (5.69)	25.43 (5.20)	24.31 (4.96)

†Pre-dialysis values; *p<0.05 indicates a difference between-groups based on Chi square Test, $^{‡,§}p$<0.05 indicates a between-group difference based on Bonferroni Post Hoc. DD: dedicated dietitian, EP: existing practice; THD: trained hospital dietitian; SD: standard deviation; HD: hemodialysis; PTH: parathyroid hormone; CaP: calcium-phosphorus byproduct; MIS: malnutrition-inflammation score; BMI: body mass index.

SERVICES USE

During Phase I, DD group consumed more services than other groups (especially emergency hemodialysis, specialist physician consults, several medications and hospitalization). THD group used more professional home care and lost more productivity hours. EP group used more informal care. During Phase II, DD group consumed a greater volume of emergency hemodialysis, specialist physician consults, sevelamer, and erythropoietin. THD group consumed more calcium carbonate, professional home care and lost more productivity hours (Table 2).

Between Phase I and Phase II, DD group showed the greatest decline in the use of the most costly healthcare services. The volume of emergency hemodialysis decreased by 44% compared with 18.6% and 16.8% in the EP and THD groups, respectively. The consumption of sevelamer decreased by 51.1%, relative to 32.2% in the EP group and to an increase of 29.8% in THD. Hospitalization days decreased by 48.4% in DD compared with 11.9% and 2% in EP and THD groups, respectively. DD group also exhibited the slowest increase in the use of patient and family-related services (+7.44% vs. +57.6% and +19.6% for DD, EP and THD, respectively).

COSTS

The cost distribution of the 3 groups is displayed in Appendix S4. As per Table 3, societal, healthcare, patient and family-related costs differed between-groups. The mean cost of the nutrition education was the highest in DD group; yet the cost of this intervention represented less than 1% of the societal costs of each of the three groups during both study phases.

The mean total societal costs were the highest in the DD group. Similarly, the mean healthcare costs were higher in the DD group. THD group had higher mean costs to patients and family. While, during Phase I, social costs were the highest in DD group, THD had the highest costs during Phase II.

Between Phase I and Phase II, DD group exhibited the highest mean decrease in costs (-\$2,226.4) (EP: -\$1,320.8; THD: -\$654.6). This was remarkably noted for costs of emergency hemodialysis (-\$51 vs. -\$11.5 vs. -\$2.4), medications (-\$419.9 vs. -\$61.0 vs. -\$58.5) and hospitalization (-\$1,151.0 vs. -\$1,010 vs. -\$310.6) costs.

Table 2. *Services use during the 12-month period*

	DD group (n=107)			EP group (n=112)			THD group (n=257)		
	Users	**Mean**	**Median**	**Users**	**Mean**	**Median**	**Users**	**Mean**	**Median**
				PHASE I					
Healthcare sector costs									
HD									
HD (session)	107 (100)	72.4	78.0	112 (100)	67.6	78.0	257 (100)	75.6	78.0
Emergency HD (session)	39 (36.4)	1.2	0.0	21 (18.6)	0.4	0.0	9 (3.5)	0.1	0.0
Healthcare professionals									
Specialist physician (contact)	28 (26.2)	0.7	0.0	26 (23.2)	0.4	0.0	62 (24.1)	0.4	0.0
Dietitian (contact)	1 (0.9)	0.0	0.0	0 (0)	0.0	0.0	21 (8.2)	0.1	0.0
Psychologist (contact)	0 (0)	0.0	0.0	0 (0)	0.0	0.0	0 (0)	0.0	0.0
Medications									
Calcium Carbonate (Tablet)	80 (74.8)	563.5	549.0	89 (79.5)	478.5	366.0	174 (67.7)	402.6	213.5
Calcium Acetate (Tablet)	43 (40.2)	288.0	0.0	39 (34.8)	236.0	0.0	108 (42.0)	299.6	0.0
Sevelamer (Tablet)	32 (30.0)	226.6	0.0	26 (23.2)	74.2	0.0	55 (21.4)	84.5	0.0
Cinacalcet (Tablet)	1 (0.9)	15.4	0.0	0 (0)	0.0	0.0	0 (0)	0.0	0.0
Active Vitamin D (Capsule 100 mL)	63 (58.9)	4.5	0.4	64 (57.1)	3.0	0.7	136 (52.9)	4.9	1.4
Vitamin D (Tablet)	33 (30.8)	15.4	0.0	26 (23.2)	9.2	0.0	55 (21.4)	8.7	0.0
Vitamin B complex (Injectable Solution)	71 (66.4)	47.9	72.0	60 (53.6)	26.1	15.1	97 (37.8)	19.1	0.0
Iron (Tablet)	36 (33.6)	51.3	0.0	36 (32.1)	36.4	0.0	59 (23.0)	40.0	0.0
Intravenous Iron (Injectable Ampoule)	72 (67.2)	13.6	12.0	78 (69.6)	13.7	12.0	146 (56.8)	9.2	6.0
Erythropoietin (Various)	85 (79.4)	170247.5	192000.0	80 (71.4)	138900.0	144000.0	198 (77.0)	131901.4	96000.0
Hospitalization (Day)	48 (44.9)	4.6	0.0	39 (34.8)	2.8	0.0	82 (31.9)	2.3	0.0
Professional home care (Hour)	3 (2.8)	0.1	0.0	3 (2.6)	0.0	0.0	5 (1.9)	12.4	0.0
Costs to patient and family									
Informal care (Hour)	51 (47.7)	94.4	0.0	53 (47.3)	115.6	0.0	113 (44.0)	62.1	0.0
Productivity losses (Hour)	70 (65.4)	192.2	56.0	59 (52.7)	99.3	10.0	167 (65.0)	291.7	48.0
Costs in other sectors									
Travel (Trip)	107 (100)	144.8	156.0	112 (100)	135.1	156.0	257 (100)	151.1	156.0

	DD group (n=93)			EP group (n=93)			THD group (n=217)		
	Users	Mean	Median	Users	Mean	Median	Users	Mean	Median
				PHASE II					
Healthcare sector costs									
HD									
HD (session)	93 (100)	72.7	78.0	93 (100)	67.7	78.0	217 (100)	75.5	78.0
Emergency HD (session)	27 (29.0)	0.7	0.0	17 (18.3)	0.3	0.0	9 (4.15)	0.1	0.0
Healthcare professionals									
Specialist physician (contact)	35 (37.6)	0.8	0.0	26 (28.0)	0.4	0.0	60 (27.6)	0.5	0.0
Dietitian (contact)	0 (0)	0.0	0.0	1 (1.1)	0.0	0.0	1 (0.5)	0.0	0.0
Psychologist (contact)	0 (0)	0.0	0.0	0 (0)	0.0	0.0	0 (0)	0.0	0.0
Medications									
Calcium Carbonate (Tablet)	58 (62.4)	479.0	366.0	65 (69.9)	491.8	366.0	102 (47.0)	339.0	0.0
Calcium Acetate (Tablet)	21 (22.6)	207.9	0.0	19 (20.4)	146.4	0.0	81 (37.3)	314.6	0.0
Sevelamer (Tablet)	12 (12.9)	110.7	0.0	6 (6.5)	50.3	0.0	29 (13.4)	109.6	0.0
Cinacalcet (Tablet)	0 (0)	0.0	0.0	2 (2.2)	6.9	0.0	5 (2.3)	14.3	0.0
Active Vitamin D (Capsule 100 mL)	46 (49.4)	4.5	0.0	38 (40.9)	3.4	0.0	99 (45.6)	3.8	0.0
Vitamin D (Tablet)	13 (14.0)	16.3	0.0	16 (17.2)	18.3	0.0	24 (11.1)	7.0	0.0
Vitamin B complex (Injectable Solution)	54 (58.1)	37.8	14.2	42 (45.2)	30.6	0.0	75 (34.6)	16.9	0.0
Iron (Tablet)	22 (23.7)	37.8	0.0	19 (20.1)	24.2	0.0	38 (17.5)	34.4	0.0
Intravenous Iron (Injectable Ampoule)	57 (61.3)	13.8	12.0	58 (62.4)	10.6	12.0	134 (61.8)	10.5	6.0
Erythropoietin (Various)	87 (93.5)	168258.1	192000.0	81 (87.1)	121633.5	96000.0	189 (87.9)	1451006.0	96000.0
Hospitalization (Day)	38 (40.8)	2.4	0.0	20 (21.5)	2.5	0.0	58 (26.7)	2.2	0.0
Professional home care (Hour)	6 (6.5)	3.2	0.0	2 (2.2)	0.0	0.0	8 (3.7)	12.0	0.0
Costs to patient and family									
Informal care (Hour)	53 (55.2)	322.3	144.0	49 (52.7)	302.2	30.5	84 (38.7)	186.3	0.0
Productivity losses (Hour)	56 (60.2)	206.5	16.0	55 (59.1)	156.4	12.0	146 (67.6)	349.0	208.0
Costs in other sectors									
Travel (Trip)	93 (100)	145.4	156.0	93 (100)	135.3	156.0	217 (100)	151.0	156.0

DD: dedicated dietitian, EP: existing practice; THD: trained hospital dietitian; HD: hemodialysis.

Table 3. *Costs during the 12-month period (US$2015)*

	DD group (n=116)		EP group (n=130)		THD group (n=299)	
	Mean	**Median**	**Mean**	**Median**	**Mean**	**Median**
			PHASE I			
Healthcare sector costs						
HD	7023.6*	7636.6	6512.8*†	7636.6	7182.7†	7636.6
Maintenance HD	6911.0*	7636.6	6477.3*†	7636.6	7173.6†	7636.6
Emergency HD	112.6*†	0.0	35.4*	0.0	9.2†	0.0
Healthcare professionals	31.3	0.0	26.4	0.0	20.8	0.0
Medications	1938.9*†	1898.5	1331.6*	1362.3	1339.7†	1279.5
Hospitalization	1738.7*	0.0	1564.6^	0.0	801.0*†	0.0
Professional home care	2.0	0.0	0.6	0.0	210.1	0.0
Total	10463.9*†	9899.3	8877.8*	8153.9	9014.8†	8740.8
Costs to patient and family						
Informal care	155.0	20.2	195.0	20.2	118.1	40.3
Productivity losses	364.3	122.3	194.0*	34.9	493.5*	134.4
Total	510.3	307.1	388.9*	147.4	611.6*	285.0
Costs in other sectors						
Travel	395.9	436.0	376.3*	436.0	421.5*	436.0
Intervention costs	74.5*†	76.9	2.6*‡	2.6	13.3†‡	13.7
Total societal costs	11724.2*†	10697.3	10203.8*	9544.8	10600.9†	10102.3
			PHASE II			
Healthcare sector costs						
HD	6015.9	7484.3	5718.2*	6385.6	6423.3*	7484.3
Maintenance HD	5954.3	7484.3	5694.3*	6385.6	6416.5*	7484.3
Emergency HD	61.6*†	0.0	23.9*	0.0	6.8†	0.0
Healthcare professionals	53.7*	0.0	13.1*	0.0	24.9	0.0
Medications	1519.0	1762.3	1270.6	1431.4	1281.2	1028.1
Hospitalization	587.7	0.0	554.6	0.0	490.4	0.0
Professional home care	61.2	0.0	0.5	0.0	140.4	0.0
Total	8237.5	9220.6	7557.0	7382.7	8360.2	8571.7
Costs to patient and family						
Informal care	429.7*	32.5	367.4	2.9	228.9*	0.0
Productivity losses	352.2	38.5	216.6*	14.0	526.8*	119.8
Total	781.9	328.2	584.0	135.8	755.7	237.0
Costs in other sectors						
Travel	338.7	427.3	333.1*	364.6	375.1*	427.3
Intervention costs	2.2*	2.6	2.1†	2.6	4.2*†	5.2
Total societal costs	9360.2	10270.0	8475.2	8709.8	9495.2	9656.5
			TOTAL COSTS			
Healthcare sector costs						
HD	1309.5	15121.0	12231.0*	13911.9	13606.0*	15121.0
Maintenance HD	12865.3	15121.0	12171.7*	13871.7	13590.0*	15121.0
Emergency HD	174.2*†	67.0	59.3*‡	0.0	16.0†‡	0.0
Healthcare professionals	85.1	20.5	39.5	16.6	45.8	14.7
Medications	3457.9*†	3341.1	2602.3*	2555.5	2620.9†	2318.0
Hospitalization	2326.3*	603.5	2119.2	445.8	1291.5*	199.4
Professional home care	63.2	0.0	1.1	0.0	350.5	0.0
Total	18972.0*	19070.3	16993.1*	17358.1	17914.7	17593.3
Costs to patient and family						
Informal care	584.7*	251.5	552.3†	161.2	346.9*†	116.6
Productivity losses	716.5*	415.1	410.6†	144.0	1020.3*†	581.4
Total	1301.2	998.1	972.9*	526.8	1367.3*	783.4
Costs in other sectors						
Travel	734.6*	863.3	709.3†	750.3	796.6*†	863.3
Intervention costs	76.7*†	79.5	4.6*‡	5.2	17.4†‡	18.8
Total societal costs	21007.7*	21548.0	18675.4*	18721.3	20078.6	19826.6

*,†,‡ $p<0.05$ indicates a between-group difference based on Bonferroni Post Hoc.
DD: dedicated dietitian, EP: existing practice; THD: trained hospital dietitian; HD: hemodialysis.

STUDY OUTCOMES

During Phase I, mean adjusted serum phosphorus decreased in the DD (-0.58 mg/dL) and EP (-0.09 mg/dL) groups; and remained unchanged in THD. During Phase II, mean serum phosphorus increased in all groups. This increase was most accentuated in the DD and EP (+0.26 and +0.25 mg/L, respectively) than the THD group (+0.04 mg/dL). At the end of the study, EP group had the highest mean serum phosphorus. Moreover, mean serum phosphorus in the EP and THD groups was higher than baseline values, in contract to DD group. At each study phase, EP group had the highest mean QALY; and by the end of the study, it gained the most QALYs (Table 4).

Table 4. *Study outcomes (mean (SD))*

	DD (n=116)	EP (n=130)	THD (n=299)
PHASE I			
Phosphorus†‡ (mg/dL)	4.99 (0.98)*	5.30 (1.17)*	5.16 (0.89)
QALY†	0.2781 (0.0436)	0.2809 (0.0419)	0.2759 (0.0441)
PHASE II			
Phosphorus†‡ (mg/dL)	5.25 (1.39)	5.55 (1.75)*	5.20 (0.97)*
QALY†	0.2570 (0.0877)	0.2620 (0.0844)	0.2609 (0.0797)
Total			
QALY†	0.5352 (0.1233)	0.5429 (0.1207)	0.5368 (0.1185)

†Imputed values; ‡Regression-based adjusted values; *p<0.05 indicates a between-group difference based on Bonferroni Post Hoc.
DD: dedicated dietitian, EP: existing practice; THD: trained hospital dietitian; SD: standard deviation.

COST-EFFECTIVENESS AND COST-UTILITY ANALYSES

In the base-case CEA (Table 5), in comparison with EP protocol, the ICER of DD for total societal costs per 1 mg decrease in serum phosphorus was $7,853.6. On the other hand, THD protocol dominated DD (i.e. DD group had higher serum phosphorus and higher societal costs). THD protocol was likely to be the most cost-effective. In the CUA, DD protocol was dominated by EP and THD protocols. Even for the highest WTP threshold, the probability that DD protocol being cost-effective is almost null. EP protocol had the highest probability of being cost-effective (Figure 1).

Table 5. *Incremental cost-effectiveness and utility-ratios*

	DD vs. EP			DD vs. THD		
	Incremental effects	**Incremental costs**	**ICER**	**Incremental effects**	**Incremental costs**	**ICER**
Serum phosphorus (mg/dL)						
*Base-Case**	-0.31	+2404.5	7853.6†	+0.05	+988.4	Dominated
*Complete cases**	-0.41	+2555.2	6248.5†	-0.02	+1049.8	59425.9†
HD costs excluded*	-0.31	+1685.6	5505.5†	+0.05	+1775.2	Dominated
*P>5.5 mg/dL**	-0.73	+4295.6	5887.4†	-0.004	+1175.2	265243.2†
Decrease in P (Detla adjustment)	-0.40	+2404.5	5935.9†	-0.11	+988.4	9212.8†

	DD vs. EP			DD vs. THD		
	Incremental effects	**Incremental costs**	**ICER**	**Incremental effects**	**Incremental costs**	**ICER**
QALY						
Base-Case	-0.01	+2404.5	Dominated	-0.002	+988.42	Dominated
Complete cases	-0.01	+2555.2	Dominated	+0.002	+1049.8	449603.7
HD costs excluded	-0.01	+1685.6	Dominated	-0.002	+1775.2	Dominated
P>5.5 mg/dL	+0.02	+4295.6	192938.1	-0.01	+1175.2	Dominated
*Adjusted QALY**	-0.01	+2404.5	Dominated	-0.003	+988.4	Dominated

*Regression-based adjusted values; †Absolute values are presented, given that the beneficial outcome is the decrease in serum phosphorus, resulting in a negative ICER.
DD: dedicated dietitian, EP: existing practice; THD: trained hospital dietitian; ICER: incremental cost-effectiveness ratio; HD: hemodialysis; P: serum phosphorus; QALY: quality-adjusted life-year.

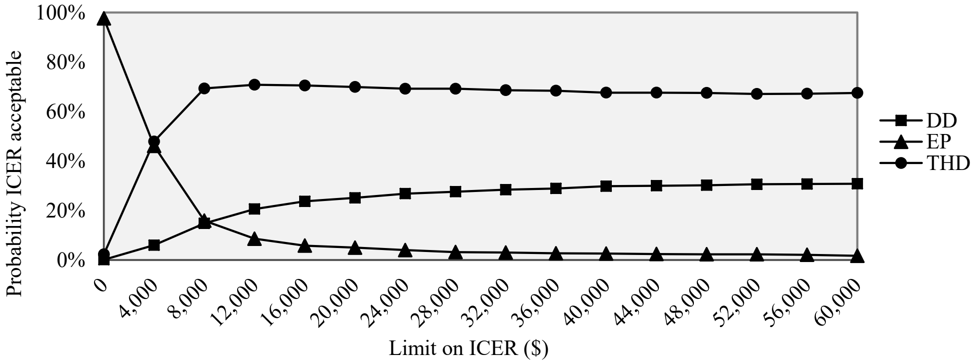

Figure 1a. *Cost-effectiveness acceptability curve presenting the probability of the protocol is cost-effective (y-axis) with respect to serum phosphorus, given various ceiling ratios for willingness-to-pay (x-axis).*
The ICER was represented in absolute values, given that the beneficial outcome is the decrease in serum phosphorus, resulting in a negative ICER. DD: dedicated dietitian, EP: existing practice; THD: trained hospital dietitian; ICER: incremental cost-effectiveness ratio.

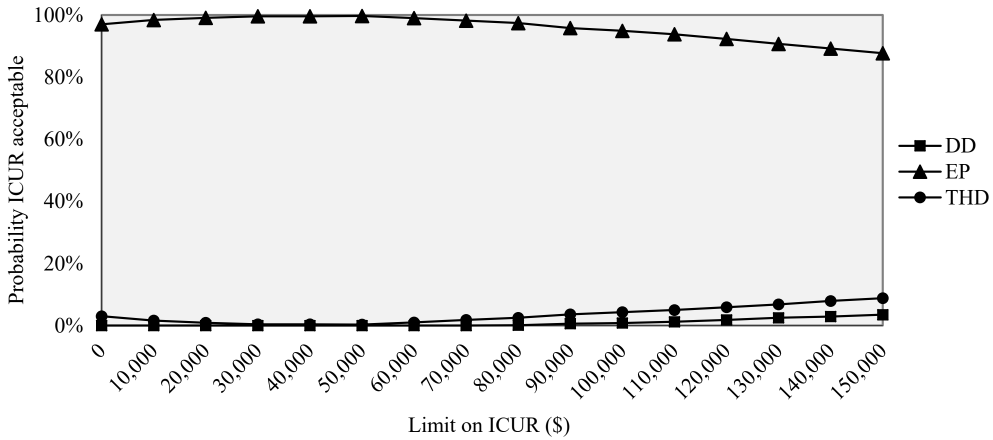

Figure 1b. *Cost-utility acceptability curve presenting the probability the protocol is cost-effective (y-axis) with respect to quality-adjusted life-year gain, given various ceiling ratios for willingness-to-pay (x-axis).*
DD: dedicated dietitian, EP: existing practice; THD: trained hospital dietitian; ICUR: incremental cost-utility ratio.

SENSITIVITY ANALYSES

The results of the cost-effectiveness and cost-utility of three protocols were inconclusive (Table 5). Regarding serum phosphorus, for all scenarios, the ICER of DD vs. EP was lower than the base-case result, thus more cost-effective. When compared with THD, the ICER of DD ranged between $9,212.8 for the delta adjustment, and $265,243.2 for hyperphosphatemic cases. THD protocol had the highest probability of being cost-effective for hyperphosphatemic patients and when hemodialysis and transportation costs were excluded. For the delta adjustment, and for complete cases, the probability of DD and THD being cost-effective tied at $8,000 and $60,000, respectively; above these values, DD was the most cost-effective protocol (Appendix S5).

Regarding QALY, DD protocol was dominated by EP for all scenarios, expect for hyperphosphatemic cases, and by THD for all scenarios, except for complete cases. Even for the highest suggested WTP threshold, the probability of DD protocol being cost-effective was low. EP was the most cost-effective protocol (Appendix S6).

DISSCUSSION

In this study, we explored the cost-effectiveness of intensive nutrition education provided by trained dedicated dietitians (DD), compared with the existing practice (EP) in Lebanon- where dietitians have limited knowledge about renal nutrition and no dietitian-to-patient contact time is set, and to another protocol (THD) where dietitian education is ensured, yet contact time with patients is not established.

The results showed that the direct costs of the nutrition education are extremely low compared with the costs of other interventions incurred as part of the management of hemodialysis patients. At the end of the study, in comparison with EP and THD groups, DD group exhibited the greatest decrease in serum phosphorus, no difference in QALY, and the highest societal costs.

Regarding serum phosphorus management, DD protocol was likely to be cost-effective compared with EP. However, it is very difficult to draw a firm conclusion of this analysis, since we lack a societal WTP threshold for decrease in serum phosphorus. The results were inconclusive in comparison with THD. Regarding QALY, DD protocol was dominated by both of the other protocols, in most of the cases. When DD was not dominated (the case of hyperphosphatemic patients in comparison with EP, and complete cases in comparison with THD), it was associated with a cost per QALY gained higher than what is considered to be an efficient use of finite healthcare resources [32,34,35]. The probability of DD being cost-effective was low for the base-case and sensitivity analyses.

Several factors might explain these results. At baseline, DD group had the highest MIS and serum phosphorus. High MIS predicts increased mortality, days and frequency of hospitalization, as well as lower QoL [36–39]. High serum phosphorus is associated with the same deleterious consequences [2–5,40]. This suggests higher baseline costs of DD compared with the other groups. This might also explain the greater decline in resources use and costs (notably for hospitalization and medications, especially costly phosphate binders) after the implementation of the intervention (Phase II). Within this scope, it is worthy to note that despite achieving a greater serum phosphorus decrease in comparison with THD (-0.32 vs. +0.04 mg/dL), mean serum phosphorus of the DD group remained higher, causing it to be dominated in the base-case analysis. The contradictory results between this analysis and the one using the delta adjustment illustrate this observation. Moreover, patients in the DD group might have been more critically ill than those in the other groups, as exhibited by the high mortality rate even before enrollment in the study. In addition, as mentioned in Karavetian et al. [14] the effectiveness of the DD protocol might have been partially "masked" by the improvement noted in the EP group, where contamination of information through patients and nurses and passive education through posters and distribution of educational material took place; and in THD group where the intervention was sustained during Phase II, in contrast to the DD group, where the intervention was stopped.

The sensitivity analysis demonstrated uncertainty in the cost-effectiveness of the DD protocol. In particular, we were not able identify whether the nutrition education is an economically attractive intervention among hyperphosphatemic patients and contradictory results were obtained regarding serum phosphorus and QALY. This finding is not in line with results from a previous economic evaluation of phosphate binders [41] which revealed better cost-effectiveness with increasing serum phosphorus- taken the accentuated morbi-mortality risk with hyperphosphatemia. The limited time horizon in our study (1 year vs. lifetime in Brennan et al. [41]) might explain this contradictory finding, as it did not allow us to explore future decrease in mortality and morbidity with better phosphorus control due to the nutrition education.

Our analysis depended on numerous assumptions and have several limitations. First, although we resorted to adjustments for baseline differences in key parameters of the economic evaluation (serum phosphorus and utility), we were not able to adjust our analysis for all baseline differences between the three groups, notably the malnutrition-inflammation status. Second, we did not collect cost data at baseline, assuming that the cluster randomization would results in similar groups; however, this was not the case and groups ended having different baseline key variables, and potentially different resource consumption characteristics. Exploring baseline costs might have explained the higher costs in the DD group. Third, the most important assumptions in our analysis related to attrited cases. We used patient-specific values when available from a previous time-point, and followed the imputation by the mean using the most detailed values, where data from a previous time-point were unavailable. We assumed that is the most feasible method in light of the limited number of patients in each group in each unit, although it might not be the most robust one. The results were sensitive to this parameter and ICERs/ICURs varied between the base-case analysis and when only complete cases were included. Potentially, attrited patients had different resource-consuming characteristics than the ones who finished the trial. A post-hoc analysis addressing this issue might provide an answer to this question. In addition, we assumed that death or hospitalization took place at the mid-point of each phase, that costs and serum phosphorus followed a linear evolution throughout time, that patients maintained their QoL at withdrawal, and applied our analyses accordingly. We adopted these method because costs, serum phosphorus and QoL values were not available at time of attrition; and due to the lack of studies describing the evolution of costs, serum phosphorus and QoL mainly before death, transfer and transplant… in hemodialysis patients. Fourth, as discussed in Rizk et al. [22] the estimation of resources consumption used a self-reported questionnaire- rather than documented sources (patient or facility records). This potentially leads to recall bias or poor understanding of the questions among patients with limited cognitive skills. Valuation of some resources costs also relied on information collected from patients, due to the lack of a manual for cost analysis in healthcare research in Lebanon. In an attempt to overcome these two limitations, the resource utilization questionnaire used in this study was designed following good practices for improved accuracy [42]. Fifth, economic evaluations of interventions targeting hyperphosphatemia management in hemodialysis patients usually adopt a time horizon longer than the one adopted in this study, in order to capture the long-term effect of reducing serum phosphorus [11]. In fact, the time horizon should be long enough to include all relevant costs and outcomes of the intervention [43]. This was not the case of our analysis, and exploring this issue through a model-based analysis adopting a lifetime horizon is needed, especially that DD protocol was associated with the best clinical outcomes and greatest decrease in societal costs in post-implementation. Additionally, it is worthy to note that the cost of the intervention is expected to further decrease on the long run, taken that the initial training of the dietitians (≈10% of the cost of DD intervention) is a one-time intervention. Finally, differences in healthcare systems funding, costs of healthcare and other resources, and societal WTP for health interventions, among other factors, limit our ability to directly generalize our results to other countries.

The primary strength of this analysis is that it used patient-level data from a randomized controlled trial; and tried to compare a novel intervention with the existing practice, and to another alternative, that could be considered as a first step towards implementing evidence-based care for hemodialysis patients in Lebanon. In addition, NEMO was conducted following a practical fashion, increasing the likelihood of the generalizability of its results to real-world practice; and its economic evaluation was performed from the preferred (societal) perspective.

According to the National Kidney Registry, nearly 3,300 patients receive hemodialysis in Lebanon [44]. The monthly budget implications of making dedicated dietitians available for all patients would be substantial (≈$40,000). Yet, a closer look at the cost savings of this intervention are also likely to be quite substantial, making this intervention worthy of an exhaustive evaluation and possibly of its consideration as part of the management of hemodialysis patients. For instance, the difference in the mean decrease in societal costs between DD and EP ($636.3) and between DD and THD ($1,258.3) in post-implementation, would offset more than 8 and 16 times the cost of the 6-month nutrition education, respectively.

Finally, this CEA assessed dedicated dietitians providing education targeting serum phosphorus. This is one aspect of the medical nutrition therapy of renal patients; and exploring other outcomes of the dietetic management is recommended, especially that previous evidence suggest substantial costs savings of nutrition interventions among renal patients through malnutrition prevention and management [45] and improved QoL [46,47]. Future clinical studies should investigate the impact of nutrition education on relevant clinical endpoints (i.e. morbidity and mortality), and CEA should assess equitable groups at baseline using an extended time horizon, to have a more realistic evaluation of the economic attractiveness of this intervention. While healthcare funding decisions must be made using the best currently available data, it is possible that future estimates of the cost-effectiveness of the nutrition education may differ.

PRACTICAL IMPLICATIONS

The additional costs of the nutrition education were low as compared with the total societal costs of hemodialysis patients. Regarding serum phosphorus, DD protocol is likely to be cost-effective compared with EP, and the probability of DD being cost-effective compared with THD protocol was low. No effect of DD was noted on QALY, and the intervention was therefore dominated in terms of cost per QALY gained.

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Appendix S1: Resource utilization questionnaire

<table>
<tr><td>1</td><td>What is your insurance/3rd party payer?
□NSSF □ MOPH □ Army □COOP □Private □Other…………………</td></tr>
<tr><td>2</td><td>In the past 6 months, how often have you contacted a specialist physician (like a cardiologist &/or endocrinologist &/or surgeon &/or …….)?----------------------
How much did it cost per visit?------------------------
How much of it did you pay from your pocket?------------------------</td></tr>
<tr><td>3</td><td>In the past 6 months, how often have you contacted your dietitian?----------------------
How much did it cost per visit?------------------------</td></tr>
<tr><td>4</td><td>In the past 6 months, how often have you contacted a psychologist?----------------------
How much did it cost per visit?------------------------</td></tr>
<tr><td>5</td><td>In the past 6 months, how many nights have you spent in the hospital?----------
How much did it cost per day?---
How much of it did you pay from your own pocket? ---------------------------------</td></tr>
<tr><td>6</td><td>In the past 6 months, how many times did you have to go for an extra emergency hemodialysis session? --</td></tr>
<tr><td>7</td><td>List the number of medications that you are prescribed in the past 6 months
<table>
<tr><td></td><td>Calcium carbonate</td><td>Calcium acetate</td><td>Sevelamer</td><td>Cinacalcet</td><td>Vitamin D</td></tr>
<tr><td>How many pills per day</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>Active Vitamin D</td><td>Vitamin B complex</td><td>Iron Pills</td><td>IV iron</td><td>Erythro-poietin</td></tr>
<tr><td>How many pills per day</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
For which one of them did you pay from your own pocket (were not reimbursed) in the past 6 months?</td></tr>
<tr><td>8</td><td>In the past 6 months, how many hours per week on average did you need family/ friends to take care of you or help you due to your health situation?------------------------
How much did it cost per hour?------------------------</td></tr>
<tr><td>9</td><td>In the past 6 months, how many hours per week did you need home care professionals (paid help) like home nurses or home doctors….?
How much did it cost you?------------------------</td></tr>
<tr><td>10</td><td>In the past 6 months, how many days were you unable to perform your daily activities due to your health (for example, days lost from work or school, days where you were unable to perform domestic work)?------------------------</td></tr>
</table>

Appendix S2: Costing of the nutrition education

Table 1. *Cost components and mean costs per patient of the three protocols (LBP)*

	#	Unit	Cost	Unit	Phase I	Phase II
Dedicated Dietitian protocol						
1) Dietitian training[a]					12055.34	0
2) Educational material[b]	78	papers	50.00	LBP/paper	3900.00	0
3) Nutrition education	12	hours (2hours/ month/6months)	7526.88	LBP/hour	90322.58	0[c]
4) Standard dietetic care	0.5	hour (1 hour/ year)[c]	7527.88	LBP/hour	3763.94	3763.94
Total					**110041.87**	**3763.94**
Existing Practice protocol						
Standard dietetic care	0.5	hour (1 hour/ year)[d]	7527.88	LBP/hour	**3763.94**	**3763.94**
Trained Hospital Dietitian protocol						
1) Dietitian training[a]					12055.34	0
2) Nutrition education	1	hour (2 hours/ year)[e]	7526.88	LBP/hour	7526.88	7526.88
Total					**19582.23**	**7526.88**

[a]Including training cost and cost of dietitian time for attending the training. Rational and conduct of the training was described in Karavetian & Rizk (2016). Training cost per dietitian, obtained from its provider (MK who is a co-author of this article), was multiplied by the number of dietitians needed to provide the nutrition education and divided by the number of patients. Dietitian cost per hour was obtained from the Syndicate of Dietitians in Lebanon (personal communication) and from a national survey among Lebanese hospital dietitians (Karavetian et al., 2013)
[b]Obtained from the provider of the training (MK who is a co-author of this article)
[c]Intervention was stopped during Phase II
[d]Mean number of hours as per the standard care in Lebanon (Karavetian et al., 2013)
[e]Mean number of hours allocated to patients in the group (unpublished data).

The costs gathered and calculated in LBP were converted to US$ (1 US$= 1507.5 L.L.; year of reference: 2011) (BDL, 2016) and uprated to 2015US$ using Consumer Price Indices (Index, 2010=100) (OECD, 2016). The costs of the dietetic interventions for the DD, EP and THD groups for Phase I and Phase II were as follows: $74.5, $2.2; $2.6, $2.1; and $13.3, $4.2, respectively.

Appendix S3: Flow diagram of the trial

A total of 720 patients participated in the study. 570 of those met the inclusion criteria.

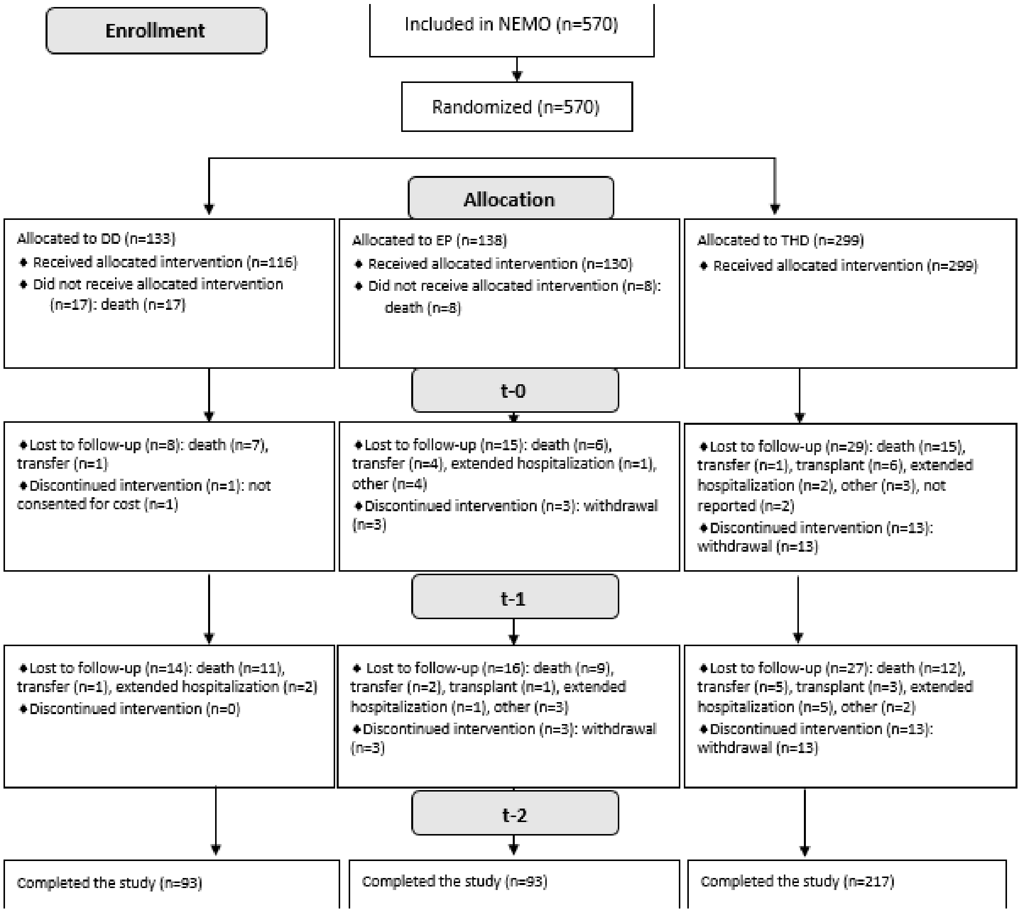
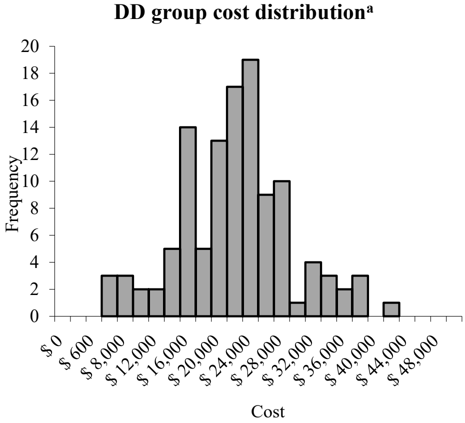
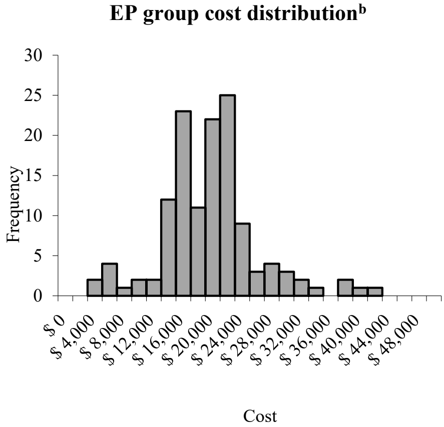


Figure 1. *Flow diagram of the trial.*

Appendix S4: Cost distribution of the study groups





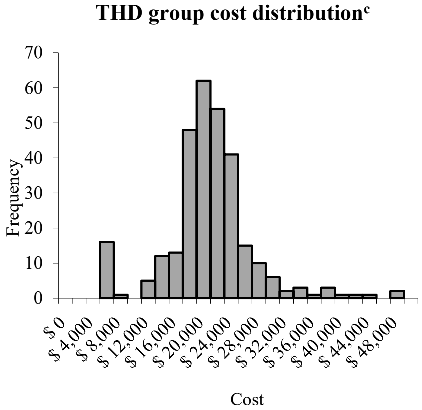
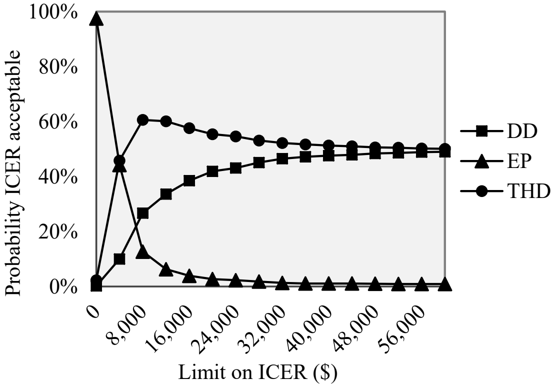


Figure 2. *Cost distribution of the study groups.*

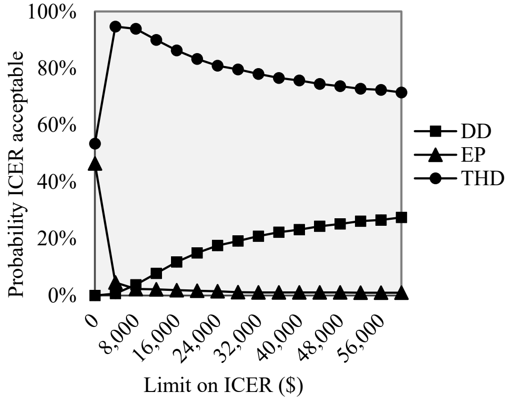
[a]DD (dedicated dietitian): 2.5th percentile: \$19,799.49; 97.5th percentile: \$22,377.03
[b]EP (existing practice): 2.5th percentile: \$17,556.73; 97.5th percentile: \$19,843.65
[c]THD (trained hospital dietitian): 2.5th percentile: \$19,325.09; 97.5th percentile: \$20,871.02.

Appendix S5: Cost-effectiveness acceptability curves for sensitivity analyses

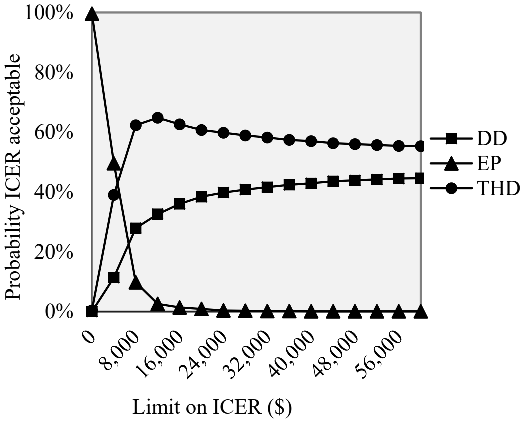
Complete cases



Hemodialysis costs excluded



Hyperphosphatemia at baseline



Difference in serum phosphorus

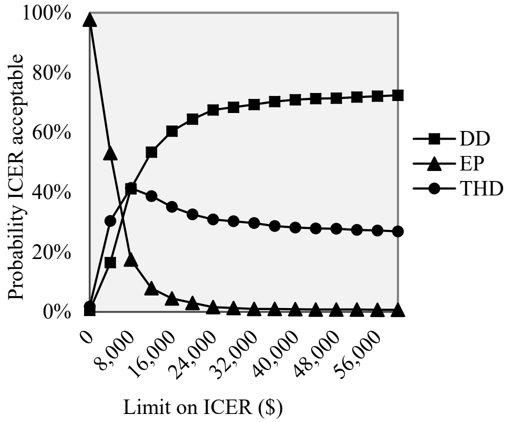


Figure 3. *Cost-effectiveness acceptability curve presenting the probability the protocol is cost-effective (y-axis), with respect to serum phosphorus, given various ceiling ratios for willingness-to-pay (x-axis).*

Sensitivity analyses performed for complete cases, hemodialysis and transportation costs excluded, hyperphosphatemia at baseline and difference in serum phosphorus as outcome. The ICER was represented in absolute values, given that the beneficial outcome is the decrease in serum phosphorus, resulting in a negative ICER. DD: dedicated dietitian, EP: existing practice; THD: trained hospital dietitian; P: serum phosphorus; HD: hemodialysis; ICER: incremental cost-effectiveness ratio.

Appendix S6: Cost-utility acceptability curves for sensitivity analyses

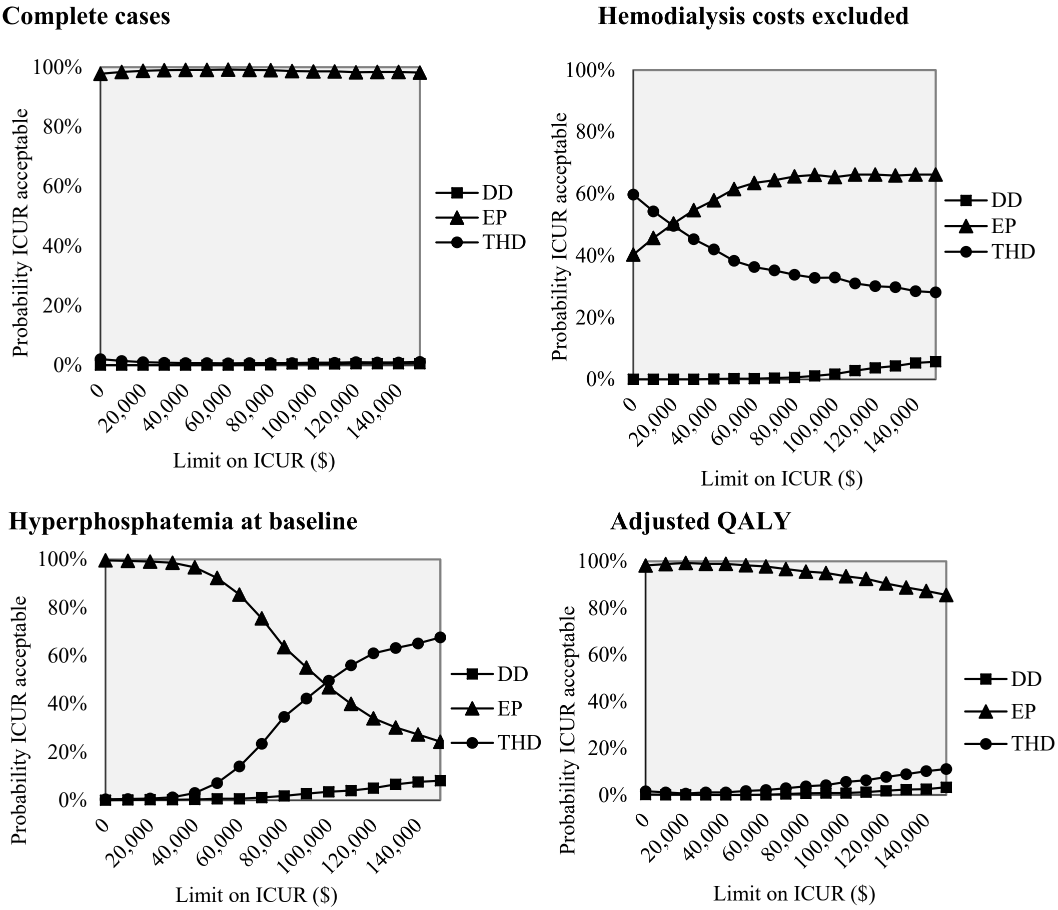


Figure 4. *Cost-utility acceptability curves presenting the probability the protocol is cost-effective (y-axis), with respect to QALY gain, given various ceiling ratios for willingness-to-pay (x-axis).* Sensitivity analyses performed for complete cases, hemodialysis and transportation costs excluded, hyperphosphatemia at baseline and adjusted QALY. DD: dedicated dietitian, EP: existing practice; THD: trained hospital dietitian; P: serum phosphorus; HD: hemodialysis; QALY; quality-adjusted life-year; ICUR: incremental cost-utility ratio.

CHAPTER

6

GENERAL DISCUSSION

In Lebanon, as in many developing and developed countries alike, managing hyperphosphatemia among hemodialysis patients remains challenging [1,2]. Given that elevated serum phosphorus is a strong and independent predictor of patient morbidity and mortality, of use of healthcare services and of costs, and given that healthcare resources are limited, this thesis aims to enhance our understanding of the health technology assessment (HTA) of hyperphosphatemia management among hemodialysis patients within the Lebanese setting. We open this chapter with a presentation of the main findings of the thesis and then discuss some of the methodological considerations. We conclude with recommendations for clinical practice, and for further research in support of public health policy making (in Lebanon).

MAIN FINDINGS OF THE THESIS

Box 1: Main findings

- Research is limited on the cost-effectiveness of phosphorus-lowering interventions among hemodialysis patients
- Calcium acetate seems to be the most cost-effective phosphate binder in first- and second-line use in hemodialysis patients
- Hemodialysis is a resource-intensive therapy in Lebanon, posing a heavy burden on the national healthcare system and on Lebanese society
- Intensive nutrition education for hyperphosphatemia management is clinically effective in decreasing serum phosphorus without compromising the nutritional status of hyperphosphatemia hemodialysis patients
- Intensive nutrition education is an inexpensive intervention within hemodialysis patient management, and is associated with a decrease in resource use and in societal costs
- Intensive nutrition education does not have any incremental effect on quality-adjusted life-years among hemodialysis patients in the short term

ECONOMIC EVIDENCE SYNTHESIS

First, in ***Chapter 2,*** we systematically reviewed full economic evaluations of phosphorus-lowering interventions among adult hemodialysis patients, published between 2004 and 2015. Twelve studies were identified, all of which reported on the comparative cost-effectiveness of phosphate binders. The majority of high-quality studies favored first- and second-line use of calcium acetate over calcium-free binders in prevalent patients. Only one high-quality study, funded by the industry, reported better cost-effectiveness of second-line lanthanum carbonate over calcium-based binders, in incident patients. We found limited evidence regarding the cost-effectiveness of calcium-free binders, and it was therefore impossible to draw firm conclusions, due to the suboptimal quality and heterogeneity of the included studies, as well as the lack of studies addressing some clinical scenarios.

Our work adds evidence regarding the limited number of cost-effectiveness studies of phosphorus-lowering interventions in hemodialysis patients and the suboptimal quality of published economic evaluations [3,4], and accordingly the need for further high-quality economic evaluations.

COST-OF-ILLNESS OF HEMODIALYSIS AND THE BURDEN OF HYPERPHOSPHATEMIA

In ***Chapter 3***, we conducted a retrospective, bottom-up, prevalence-based cost-of-illness (COI) estimate, using data from the Nutrition Education for Management of Osteodystrophy (NEMO) trial. The mean 6-month societal costs of hemodialysis were estimated at $9,258, of which 91.7% were attributable to healthcare costs, 4.2% to patient and family costs, and 4.1% to costs in other sectors. The annual costs of hemodialysis in Lebanon were estimated at $61 million and healthcare costs were estimated at $56 million. The latter represented around 1.82% of the total healthcare expenditures in Lebanon (estimated $3 billion in 2012). This study highlighted the debilitating financial burden of hemodialysis on Lebanese society and third party payers (the annual cost per patient: $18,517, being 43.7% higher than the national gross domestic product per capita). The study also provided a typical illustration of the high cost of hyperphosphatemia management through phosphate binders, especially calcium-free agents. Phosphate binders accounted for 2.3% of annual societal costs and 16.7% of annual costs for medications. Moreover, despite being used by only 23.7% of the study population, the average cost of sevelamer outweighed the combined costs of calcium carbonate and calcium acetate, which were used by 78.9% and 35.1% of the study population, respectively. We argue that the current financial burden of managing phosphatemia through phosphate binders is higher than it was in 2012, when the Nutrition Education for management of Osteodystrophy (NEMO) trial was conducted. In recent years, sevelamer and lanthanum carbonate largely penetrated the Lebanese market and are being prescribed increasingly by nephrologists in Lebanon (Personal communication with the Department of Nephrology, Ministry of Public Health, Lebanon, 2016).

CLINICAL EFFECTIVENESS OF INTENSIVE NUTRITION EDUCATION

In ***Chapter 4,*** we used the data from the NEMO trial to assess the impact of intensive nutrition education on the hyperphosphatemic subset of hemodialysis patients. The intervention resulted in an immediate significant decline in serum phosphorus in all study groups. It was the greatest among Dedicated Dietitian (DD) patients, who also solely progressed in their readiness to adhere to a low-phosphorus diet. At 6 months post-implementation, serum phosphorus remained stable in the DD and Trained Hospital Dietitian (THD) groups, yet, it increased significantly in the Existing Practice (EP) group, to levels higher than at baseline. Also, DD patients relapsed in their adherence to the low-phosphorus diet. Most importantly, throughout the trial, the malnutrition inflammation score (MIS) remained stable only in the DD group, in contrast to the other groups, who exhibited a significant increase, denoting a worsened nutritional status and predicting severely deleterious outcomes, such as poorer quality-of-life, increased risk of hospitalization and greater risk of death [5]. The improvement in the EP group was not expected, and the potential reasons behind it are detailed in the section for methodological considerations. Conversely, the mild improvement in the THD group was expected and may be a result of the upgraded and intensified visits of dietitians to the hemodialysis unit in comparison with their usual practice. Karavetian & Ghaddar [6] and Morey et al. [7] reported that the presence of a dietitian as an *"authoritative figure"*, and simple yet frequent interactions between the dietitian and the patients can improve serum phosphorus outcomes. Accordingly, we suggest that intensive and sustained behavioral nutrition education results in the greatest patient-driven decline in serum phosphorus. While these findings are in line with previous reviews of the literature conducted by Matteson & Russel [8], Caldeira et al. [9] and Karavetian et al. [10], our results fill in a gap within evidence-based practice guidelines [11], and provide evidence that irregular and distant follow-ups for patients participating in phosphorus-lowering dietary interventions adversely impacts their nutritional status. Maintaining good or stable nutritional status during dietary phosphate restriction requires sufficient time for careful instruction, regular counseling and close monitoring by a competent dietitian.

COST-EFFECTIVENESS OF INTENSIVE NUTRITION EDUCATION

In ***Chapter 5,*** we assessed the cost-effectiveness and cost-utility of intensive nutrition education (DD protocol) for hyperphosphatemia management among hemodialysis patients, in comparison with the existing practice (EP protocol) in Lebanon and another proposed alternative (THD protocol). The additional costs of the nutritional intervention were greatly higher in the DD group than in THD and EP. Yet, it was, in all groups at both study phases, very low in comparison with the societal costs (<0.64%), and with the costs of other resources used. For instance, the cost of phosphate binders was more than 6 times higher than that of the intensive nutrition education (sub-analysis on complete cases from the DD group). With regard to outcomes, the DD group witnessed the greatest decline in serum phosphorus, yet no differences in utility nor in quality-adjusted life years (QALY) were noted between the groups. Regarding the use of services and consequent costs, the DD group used the most services and generated the greatest total societal costs. At 6 months post-implementation of the intervention, the DD group showed a sharp decline in use of services and in societal costs; this decline was the greatest among the 3 groups. This was especially noted with regard to costly services, such as calcium-free phosphate binders, hospitalization, and emergency hemodialysis sessions. In the base-case analysis, the DD protocol was likely to be cost-effective in comparison with EP. Yet, it was dominated by THD. As for the cost-utility analysis, the DD protocol was dominated by both EP and THD. The sensitivity analyses yielded varying and inconclusive results, suggesting uncertainty in the study results.

METHODOLOGICAL CONSIDERATIONS

Box 2: Methodological considerations

- Conducting a systematic review of health economic evaluations and interpreting its results are challenging
- A direct comparison of the results of the cost-of-illness study with other countries is challenging due to methodological issues, as well as to differences in clinical and health systems, among other factors
- We lack essential elements for research in health technology assessment in Lebanon
- National guidelines for conducting and reporting health economic studies (cost-of-illness and economic evaluations) do not currently exist in Lebanon

Various methods were used in this dissertation, including a systematic review (***Chapter 2***), a COI study (***Chapter 3***), a randomized controlled trial (RCT) (***Chapter 4***) and a trial-based economic evaluation (***Chapter 5***). This section addresses the methodological challenges, strengths and limitations of these methods.

SYSTEMATIC REVIEW

Over the past decades, the understanding and management of serum phosphorus in hemodialysis patients have been transformed. Tight control of serum phosphorus was recommended by evidence-based practice guidelines [12], and the use of pharmaceutical agents, especially expensive calcium-free binders, has proliferated, on the basis of little or no additional clinical benefit [13–17]. It is thus becoming incumbent on us to conclusively demonstrate the cost-effectiveness of these agents [18], and to assess the economic value of other interventions. Systematic reviews addressing clinical questions are essential in health care. They are regarded as the highest level of evidence, are often looked upon as a starting point for developing practice guidelines and are widely recognized as critical in guiding decision makers towards implementing best health care policy and practice [19–22]. In parallel, since 1990, publishing has seen a steady flow of systematic reviews of economic analyses [23]. These reviews integrate information from multiple studies [24] and are therefore useful for synthesizing economic evidence about health interventions [25] and providing key information for policy making and HTA processes [24–26].

While we followed available recommendations for conducting and reporting on systematic reviews of economic evaluations in health care [21,27], and for appraising the quality of included studies [28], the conduct of the review faced many challenges and our results were subject to several limitations which are common to economic reviews [24,29]. These challenges are on one hand methodological, and on the other hand relate to the transferability of our results, to aid decision making across different settings. The first set of limitations could be summarized by the lack of a standard methodology for preparing systematic reviews of health economic evaluations (identification, appraisal, and synthesis of evidence), and for reporting on the results in a way most useful to end users [23,29]. These challenges were recently addressed in a series of reviews on the development of systematic reviews of economic evaluations [25,30,31]. This series also highlighted some of the limitations that we faced while conducting this review, such as the lack of standard techniques for reaching consensus between reviewers when there are disagreements regarding the inclusion of studies, on evidence synthesis and on assessing quality, as to date resolution of these disagreements relies solely on discussion between authors. Another limitation is the lack of validated tools for assessing the quality of both model-based and trial-based economic evaluations. In addition, some economic evaluations lacked adherence to methodological and reporting guidelines. This hindered evidence synthesis, the overall quality of the evidence of the review, and the explanation of potential differences between study findings. Our results are also limited by the multitude of factors surrounding the transferability of economic evaluations between countries, such the epidemiology and clinical management of hyperphosphatemia, availability and prices of health services, and different decision contexts and budget constraints [26,32]. Delineating tools to identify potential transferability, such as a score or index defining minimal methodological and structural requirements to enable health economic evaluation to be transferable to various decision making contexts could be regarded as a feasible approach [33].

The use of systematic reviews of economic evaluations in decision making seems to be hindered by behavioral and political factors, which could affect the usefulness of reviews for making decisions [34]. Potentially, interaction between researchers and policy makers to better highlight information that is relevant for decision making, involving policy makers in the production of reviews, and making the synthesized evidence available in user-friendly “front ends” are warranted to facilitate better understanding and greater use of the results of economic reviews [24,29,35]. Finally, it is worth noting that, while synthesis of health-economic evidence could inform policy makers, it cannot entirely overshadow the importance of context-specific cost-effectiveness information and the need for adapting synthesized evidence to local economic guidelines [32].

COST-OF-ILLNESS STUDY

COI studies are being conducted increasingly with the aim of highlighting the burden of the disease, over and above the usual epidemiological estimates of morbidity and mortality, helping to determine medical research priorities and providing a baseline against which new interventions can be assessed [36,37].

The findings of our COI study are in line with previous regional and international publications, highlighting the high financial burden of hemodialysis [38,39]. The annual COI of hemodialysis in

Lebanon found in our study ($18,517) was below the costs reported from high-income countries [38], and fell in the middle of the range of costs reported from other upper middle-income countries [39] (i.e. $7,608 in South Africa to $30,467 in Turkey; uprated to the year 2015). The direct comparison of our results with those of other studies is challenging. In fact, the wide variability in the annual cost estimates of hemodialysis between countries and between authors within the same country was reported in a systematic review of COI studies by Mushi et al. [39], although all of the studies reviewed followed the same Sum_Diagnosis Specific estimation method [40]. These differences can obviously be explained by the varying methodologies used, i.e. study design and costing approach, perspective adopted, type of costs and which cost items were included in the analysis. This is illustrated by the staggering difference COI of hemodialysis in South Africa (ranging between $7,608 and $25,682) [39] and in Jordan ($10,844 [41] and $22,368 [42]), for example. Yet, there are further underlying factors when benchmarking against other studies, such as the characteristics of the sample, practice guidelines and the clinical management of patients, methodological considerations (sources of information, costs of the services used, and differences in applying costing approaches), as well as country- and health system-specific issues, i.e. availability and validity of information and reimbursement mechanisms, among others. This issue is clearly illustrated when comparing our study with that of Abreu et al. [43], in Brazil.

The heterogeneity in the conduct of COI studies and lack of transparent reporting are common for dialysis [38,39,44], as well as for other diseases [37,45–48]. These factors make it challenging to compare results across studies and over time [37,45,46]. Also, the wide variation of cost estimates raises serious questions regarding the accuracy and validity of COI studies, consequently hindering their use in healthcare decision making [47,48]. For COI studies to be more robust and useful, closer agreement among researchers and strict adherence to available recommendations around "best practices" is a worthy first step [37,49–53] while waiting for guidelines on the methodology and reporting of COI studies to be published [54]. These awaited guidelines, coupled with improvement in data availability and quality, may enhance the credibility and validity of COI studies and increase their use by policy makers [48,54].

It is essential, however, to acknowledge the limitations of using COI studies in public health policy making [53]. While these studies can present a useful opportunity for communicating with the public and policy makers on the relative importance of an illness, and can foster policy debate and stimulate research and policy initiatives aiming at more cost-effective treatment and prevention of illness, without other information they cannot guide decisions on the allocation of scarce health resources [36]. Rather, for this aim, cost-effectiveness studies of health technologies should be undertaken [36]. Finally, to date there is little information on the applications and outcomes of the use of COI in real-life policy making, and the value of pertinent research on this is uncertain [48,52,55]. More discussion is needed among all stakeholders to define the most useful metrics for public and private health care decision makers, legislators, employers, insurers and providers, to identify opportunities for COI to be a good economic tool within decision making [48].

RANDOMIZED CONTROLLED TRIAL

When evaluating the effectiveness of an intervention, the RCT design is generally regarded as providing the most reliable evidence in health care. This is because this design minimizes the risk of confounding factors influencing the results, and permits elucidation of the impact of a health intervention. Accordingly, the findings of RCTs are probably closer to the true effects of a particular intervention than the findings generated by other research methods in health care [56].

Our effectiveness study was conducted using data from the NEMO trial [1], and holds the same strengths, limitations and methodological considerations. First, NEMO was implemented within the national health care setting, rather than operating in the idealized experimental environment, consequently generating “real life” useful and practical data [57]. Second, few specific exclusion criteria were applied, and the participants shared characteristics common to hyperphosphatemic hemodialysis patients reported from other areas of the world [7,58–63]. These factors suggest that the results of this study are likely to be generalizable to this patient population. The final major strength pertains to the use of the MIS to assess the nutritional status of the patients. This tool is regarded as the gold standard for assessing the nutritional status of hemodialysis patients, and is predictive of short and long-term mortality, morbidity, hospitalization and quality of life (QOL) outcomes [5,64–66]. The most important limitation of the NEMO trial pertains to the recruitment of the intervention and control groups from the same hemodialysis units, and their assignment to different protocols based on their dialysis shifts. The cluster-based randomization was obviously chosen for compelling feasibility reasons, and was used in previous research on an educational intervention among hemodialysis patients [67]. However, in our study, this design resulted in a contamination of information between DD and EP groups, which might explain the improvement in serum phosphorus in the latter group, where serum phosphorus was mimicking changes seen in the DD group, but to a lower extent. Accordingly, the cluster randomization of patients based on dialysis shifts seems not to be an effective allocation method for this patient population, given the frequent possible interaction among patients, and between them and healthcare providers, and the potential exposure of control subjects to educational material [68]. Care must be taken in future trials employing a cluster-based randomization in order to maintain the practical implementation of the trial without compromising its internal validity. Next, the second phase of the study was intended to be a follow-up phase, where the impact of removing the intervention would be assessed. However, we could not evaluate this issue in the THD group, where the trained hospital dietitians continued to provide their “upgraded” care, and it was unethical to ask them to go back to their pre-training care or to reduce the frequency of hemodialysis patients consults. Third, we tried to explain the mechanism by which the intervention was effective in reducing serum phosphorus by exploring the evolution in dietary phosphorus intake and phosphorus-to-protein ratio, but this was a challenge. The tool that we used (24-hour dietary recall) for this aim has numerous limitations in hemodialysis patients. The 24-hour recall relies on the patient's ability to remember and accurately report foods consumed, and may underestimate actual intake even when conducted by a trained interviewer, and can generate great variability in the mean daily nutrient intake [69]. This limitation should fuel the search for practical and valid tools in this regard. Fourth, we did not collect information regarding adherence to phosphate binders, which was targeted in some of the educational sessions. Previous similar studies suggested that nutrition education could contribute to an increase in the efficacy of phosphate binders by reducing the dosage needed and ameliorating compliance and tolerability [58]. This issue remains to be explored by future studies.

TRIAL-BASED ECONOMIC EVALUATION

Given the scarcity of healthcare resources, economic evaluations which compare the costs and outcomes of an innovative intervention with a control intervention (usually existing care) are explicitly being used to inform decision makers on the efficient use of available resources for maximizing health benefits. Economic studies conducted alongside randomized controlled trials, i.e. trial-based economic evaluations, are a primary source of data on the cost-effectiveness of health technologies [70,71] and their use is partial basis for health service decision making in many settings [71].

Interpreting the results of our trial-based economic evaluation was challenging. Given the striking baseline differences in key parameters, it was impossible to draw a firm conclusion about the cost-effectiveness of the DD protocol. At baseline, the DD group had the highest MIS and serum phosphorus, which reportedly predict increased mortality, days and frequency of hospitalization, as well as lower QOL [5,64–66,72–75]. These factors made it practically impossible for intensive nutrition education to be cost-effective. For instance, although the DD group achieved a greater serum phosphorus decrease in comparison with the THD group (-0.32 vs. +0.04 mg/dL), the mean serum phosphorus of the DD group remained higher, causing it to be dominated in the base-case analysis. Although we resorted to adjustments in serum phosphorus and utility, we were not able to adjust our analysis for all baseline differences between the three groups, notably the malnutrition-inflammation status. Feasible statistical means are needed to allow simultaneous multiple adjustments and the generation of patient-level data (for bootstrapping and for the construction of cost-effectiveness acceptability curves). Furthermore, as these baseline differences suggest higher baseline use of resources and costs in the DD group, it would have been wise to collect costs data at baseline, and complement our analysis with a regression-based adjustment of patient-level cost data [76]. Although it is not common to report baseline costs in trial-based economic evaluations, van Asselt et al. [76]

argued that costs at baseline would influence costs during the trial and presented the case for reporting these costs and investigating their influence, in order to be able to attribute the difference that is found afterwards to the intervention. Regarding QALY, we could not detect any incremental effect of the intervention. This might be related to the short time horizon of the study, the improvement of serum phosphorus in all study groups and its potential impact on QOL, or to the simple fact that decreasing serum phosphorus among hemodialysis patients is not associated with improvement in QOL or survival, which has not been conclusively proven. Although our results did not confirm the cost-effectiveness of intensive nutrition education, a closer look at the low cost of nutrition education, coupled with the greater decrease in use of services and in post-implementation costs would probably reveal the true added economic value of the DD protocol. The cost savings of this intervention are likely to be quite substantial, making it worthy of a thorough evaluation and possibly of considering it as part of the management of hemodialysis patients.

Finally, the performance of this economic evaluation was subject to many challenges, specifically the lack of essential elements in HTA research in Lebanon, which forced us to adopt alternative methods to circumvent these limitations. While neighboring countries have formally integrated HTA in decision making (e.g. reimbursement of drugs) and implemented some basic pertinent requirements [77,78], HTA research and applications in Lebanon are quasi-nonexistent, as the country lacks national methodological and reporting guidelines for economic evaluation and costing studies, standardized resource-use measures, country-specific utility weights, and a societal willingness-to-pay threshold. We detail these issues and discuss pertinent research and public policy implications in the following section.

IMPLICATIONS

Box 3: Implications

- Health technology assessment in Lebanon is necessary as part of the current reform of the Lebanese health sector
- A concerted effort from all stakeholders is needed to build capacities for national health technology assessment, build evidence and bridge current gaps
- It is necessary to search for cost-effective means to reduce the economic and clinical burden of hemodialysis and establish a framework linking scientific evidence to efficient national public health interventions and routine clinical practice
- High-quality research addressing the impact of hyperphosphatemia management among hemodialysis patients on hard end-points is needed
- High-quality research for cost-effective phosphate-lowering interventions in hemodialysis patients is needed

The findings of this dissertation present numerous implications for clinical practice, public health decision making, and research (especially for future local HTA). We detail these implications below.

CLINICAL PRACTICE IMPLICATIONS

Our results provide further high-quality evidence for clinicians regarding the effectiveness and "safety" of intensive behavioral nutrition education in enhancing adherence to a low-phosphorus diet and in lowering serum phosphorus levels, without compromising the nutritional status of hemodialysis patients. This approach was superior over marginal nutrition advice (existing practice in Lebanon). These findings reinforce the value of dietitians as an integral part of the nephrology care team, and shed light on their unique skills which enable them to actively and positively contribute to hyperphosphatemia management among hemodialysis patients, without the need for increased resources, other than ensuring adequate dietitian skills and sustained dietitian-to-patient time.

PUBLIC HEALTH DECISION MAKING IMPLICATIONS

Hemodialysis has been identified as a resource-intensive therapy and a major public health problem in Lebanon. With the rapidly increasing prevalence of hemodialysis in the country, the direct and indirect costs of this treatment are expected to rise. Accordingly, the search for measures optimizing hemodialysis management is crucial. By exposing the financial burden of hemodialysis and its main drivers, and by exploring the cost-effectiveness of two health technologies in this patient population i.e. phosphate binders and nutrition education, the current study provided decision makers with information for health services planning and potential cost containment initiatives. The review of the literature suggested that calcium acetate may be the most cost-effective binder and that the systematic use of calcium-free binders may not be a rational use of health resources. Rather, these agents might provide good value for money spent as second-line therapy in selected patients. The trial-based economic evaluation showed that the intensive nutrition education had a low direct cost, yet a low probability of being cost-effective. We argue that this intervention might be cost-saving, and we recommend further investigation into its cost-effectiveness. The only loss in the proposed technology is the initial training of the dietitians and their financial compensation, which is extremely inexpensive within hemodialysis patient management. We speculate that a significant reduction in the global clinical and economic burden of the disease can be achieved when this intervention is implemented in Lebanon.

Concrete implications for health technology assessment implementation in Lebanon

The Lebanese healthcare system is pluralistic and unregulated, with highly fragmented financing. The overwhelming majority of health care services and delivery units are privately owned and operated, whereby the country, especially the capital Beirut, enjoys some of the most advanced medical facilities and services in the region, and exhibits a rapid and extensive diffusion and up-take of state-of-the-art medical technologies. Over the last 20 years, the country has invested heavily in medical technologies and services, and it is a constant strategic challenge to moderate technology diffusion to the most efficient interventions. To date, major system deficiencies still limit the ability to ensure gross equity and efficiency. These include (but are not limited to) the lack of a clear policy and strategy for health care on the part of the government, the overwhelming preponderance of an unregulated private sector in the financing and provision of health care, the minimal pooling of resources with high out-of-pocket expenditures, the lack of systematic health data collection, and the unavailability of such data to the stakeholders and to the public [79].

HTA has emerged globally as a powerful tool for institutionalizing the use of evidence in health care decision making, and for promoting health equity. Accordingly, the integration of HTA within national decision making has been advocated as part of the restructuring of the present healthcare system [79,80]. The creation of a national non-executive HTA agency which will guide the HTA process (identification, priority setting, assessment, appraisal, reporting, dissemination, and implementation in policy and practice) [81] of health care technologies is suggested. The agency would establish the effectiveness of technologies and mechanisms for prioritizing them for affordability and plausible public/collective responsibility. We propose this approach, as Lebanon's experience with autonomous public bodies is not encouraging, and the concept of having an agency overseeing the Ministry of Public Health is not compatible with the administrative and legal environment and would undoubtedly be politically rejected. However, it is common and feasible that a non-executive and preferably self-financing body fills the space between formal and self-regulation in the health care sector; hence the value of creating an HTA agency [80]. The HTA agency would not only be a viable option, but is also a necessity within the current reform of the Lebanese health sector. Its feasibility is assured by the support of the government, legislature, and relevant stakeholders, both nationally and regionally.

The increasing demand for transparency and credibility in healthcare decision making in Lebanon, coupled with the growing culture of value-based care within the political and scientific communities present a unique opportunity that Lebanon should grasp for implementing national HTA [80,82]. A proposed initial step would be to map the national level of institutionalization and the current levels and trends in the HTA process, in terms of political buy-in, as well as stakeholder, human and financial capabilities. National-level mapping will provide information for assessing the feasibility of developing HTA. It is expected to provide insights regarding the ability to overcome many of the barriers associated with the initial development of a national HTA program, to help inform strategies, and to justify expenditure for HTA. Moreover, it will serve as a baseline measurement for future monitoring and evaluation [83,84].

The establishment of a successful and sustainable HTA infrastructure requires several conditions [84–89], some of which are already available in Lebanon [79,80,82]. These key conditions include a coherent and effective health policy structure, general awareness of HTA and its acceptance as a new and integrated tool for the routine evaluation of health technologies (and not a finite project or one-off exercise), an interest and strong commitment from policy makers, an ability and willingness to commit public money to HTA, support from and involvement of key stakeholders (national-level policy makers, academicians, industry experts, care providers, mass media, civil societies, and patients, among others) throughout the HTA process, adequate governance through the establishment of implementation, monitoring and evaluation mechanisms as part of a transparency and accountability framework, in addition to working toward the independent status of an HTA agency and establishing management procedures including a protocol for dealing with conflicts of interest, as well as developing scientific capability and establishing an HTA training program, and collaborating with regional and international networks, entities and organizations to benefit from their experience in building the national HTA program.

In particular, in a country like Lebanon, there might be stiff resistance to the introduction of HTA. Transparency, communication, clarity and openness, and the involvement of core stakeholders and professional bodies in the HTA process are essential for overcoming lack of trust and increasing credibility [84]. The latter factor is a crucial issue in establishing, sustaining, and using national HTA in policy making. However, international and regional experiences show that involving stakeholders cannot take place instantaneously. In fact, various stakeholders hold different interests, responsibilities, infrastructures, and barriers, all of which need to be considered, addressed and met for an HTA program to succeed. It is therefore essential to create a framework in which the ideas, needs and expectations of stakeholders are taken into account, and communication and interaction with them is assured [87,90–94].

One additional major concern in developing countries is that the results of HTA reports are not used efficiently, and incorporating their evidence into policy faces manifold barriers at both professional and public levels [85,95]. HTA information tends to be used sporadically, rather than applied in a proactive, systematic manner [91], and the use of health technologies continues to be based on their efficiency and successful performance in developed countries, without establishing their costs and efficiency at the local level, as well as their cultural, social, and infrastructural adequacy [86]. If Lebanon is set to engage in HTA, a framework for linking HTA results to policy making and implementation is needed, and a systematic approach which involves policymakers, funding bodies, and healthcare providers, improving infrastructures, and boosting supervision of performance is recommended. Delineating a clear plan at the macro level of the health system for using HTA reports, raising awareness and promoting HTA-related knowledge for all audience groups should pave the way for an effective use of the results of these projects [91,95–97].

RESEARCH IMPLICATIONS

First, the search for cost-effective means for reducing the economic and clinical burden of hemodialysis in Lebanon should be fostered. Furthermore, a framework linking scientific evidence to efficient national public health interventions and routine clinical practice should be established. The search should focus on means for preventing chronic kidney disease, and on means for preventing or slowing its progression, such as screening and early detection of chronic kidney disease, correct and timely referral to specialists and adequate medical and dietetic management of common local causes of kidney failure (including diabetes and hypertension) [98–100], as well as on approaches to increase the use of kidney transplantation [101], and other cost-effective forms of dialysis, such as home hemodialysis, where clinically indicated [102,103].

Second, research addressing hyperphosphatemia management among hemodialysis patients has seldom explored the impact of reducing serum phosphorus on hard end-points, such as mortality [18,104]. To date, the recommendation to lower serum phosphorus to a certain "target range" is based largely on cross-sectional or retrospective data [11,12], as it is unethical to randomize patients to different phosphate levels because of the observational data. Developing feasible methodologies to assess this issue in an ethical manner should be at the top of research agendas in nephrology care. Meanwhile, high-quality research on cost-effective phosphate-lowering interventions in hemodialysis patients, encompassing phosphate binders, nutrition education, various modalities of dialysis therapy, and extending other interventions, such as physical activity during dialysis, is needed. In addition, we recommend specific further research on the impact of the nutrition education on hard endpoints, such as the hospitalization, morbidity and mortality of hemodialysis patients, and on its long-term cost-effectiveness. We also suggest mapping the current nutritional status (including phosphorus control and malnutrition-inflammation status) of hemodialysis patients, as well as their use of services and associated costs, to serve as a solid basis for future monitoring and evaluation studies.

Third, the economic evaluation conducted as part of this dissertation exposed the "virgin" territory of health economic studies and the lack of infrastructure related to HTA research in Lebanon. Having local data, local technical expertise and local institutions are core requisites for establishing national HTA research [105]. Accordingly, we recommend the following: 1) delineating an explicit set of guidelines for conducting and reporting health economic studies (including economic evaluations); 2) delineating costing guidelines; 3) developing standardized resource-use measures; 4) adapting generic QOL instruments to Lebanese society; 5) generating utility weights, and 6) estimating a societal threshold for willingness-to-pay. These recommendations require a concerted effort from all stakeholders to build capacities, make investments, and bridge research gaps in national HTA evidence [92,97]. As has been done successfully in other developing countries implementing HTA research, Lebanon needs to build a core interdisciplinary team with skills in HTA, clinical medicine, health economics, clinical epidemiology, information technology, and evidence synthesis [88]. Other concrete steps include equalizing the criteria for performing HTA among Lebanese researchers, further training local expertise, establishing educational programs (MS degree) and fostering PhD research in this field, and facilitating network-building with international experts alongside scientific competence [89,106].

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VALORIZATION

The present thesis explored the health technology assessment (HTA) of hyperphosphatemia management among hemodialysis patients, with a focus on the Lebanese setting. It reviewed the evidence behind the cost-effectiveness of phosphorus-lowering interventions in this patient population; explored the cost of hemodialysis in Lebanon and its drivers; assessed the clinical effectiveness of dedicated dietitians providing nutrition education; and evaluated its cost-effectiveness in comparison with the existing practices in Lebanon.

This thesis is directed towards clinicians, policy makers and researchers, and contributes to the efforts tackling the burden of hyperphosphatemia, and aiming to offer optimal care to hemodialysis patients. This research informs decision makers about the high financial burden of hemodialysis and hyperphosphatemia management among hemodialysis patients in Lebanon, and about the effectiveness of intensive nutrition education as a phosphorus-lowering intervention. In light of the insufficient evidence about the cost-effectiveness of interventions targeting hyperphosphatemia management, this dissertation suggests the intensive nutrition education as a cost-saving solution. Finally, this thesis informs researchers about numerous gaps related to the HTA of interventions targeting hyperphosphatemia in this patient population on the international level, and about the gaps related to HTA evidence-building, specifically in Lebanon.

This research could further be considered as an initial model of incorporating clinical and economic evidence in the assessment of health technologies in Lebanon, and a first step towards adopting a transparent value-based model of care within the national healthcare system.

Although this thesis has several clinical, economic, societal, public policy and research implications discussed below, it is worthy to acknowledge its limitations (discussed in ***Chapter 6***) and the need for further studies in order to fully understand the value of the proposed technology.

PROPOSED TECHNOLOGY AND IMPLEMENTATION ROADMAP

As insightfully declared by Pronovost et al. [1] "one of the greatest opportunities to improve patient outcomes will probably come not from discovering new treatments, but from more effective delivery of existing therapies". The effective delivery of intensive nutrition education requires several key elements to be ensured: 1) expertise factor, i.e. adequate education and skills related to renal dietetics and nutrition education, requiring the translation of nutrition recommendations into core professional education programs to facilitate adoption, 2) time factor, i.e. adequate dietitian-to-patient ratio and sufficient dietitian-to-patient time, and 3) collaborative relationship with relevant organizations to support practicing dietitians in implementing renal nutrition guidelines, reduce practice variations and develop performance measures to assess compliance with the guidelines, all of which must be performed within a scientific and public policy supportive environment [2].

We propose to allocate dedicated dietitians to hemodialysis units, as a first step towards implementing renal nutrition evidence-based practice guidelines, improving patient outcomes, and possibly decreasing pertaining societal costs. We propose this health technology as an innovative and feasible model of renal nutrition care in Lebanon and other developing countries with similar healthcare systems. As recommended by evidence-based practice guidelines, renal dietitians, playing a pivotal role in the unit, should determine the nutrition diagnosis and intervention for hemodialysis patients. Within the proposed technology, every hemodialysis patient will have access to a qualified dietitian and receive intensive nutrition counseling and dietary management based on an individualized plan of care developed before or at the time of commencement of hemodialysis therapy, and modified as indicated.

Implementing this technology within hemodialysis units in Lebanon requires numerous considerations, extending from public health policy makers (system and organization), to third party payers, and to the renal nutrition and health care providers in Lebanon. We propose below a practical implementation roadmap entailing specific, concrete and actionable steps.

<u>Governance considerations</u>

- *Health systems arrangements*

There is no specific description of the required dietetic care for hemodialysis patients in the Lebanese Healthcare Organizations Accreditation Law. Clinical duties of the hospital dietitian are limited to provision of evidence that the dietitian responds to requests to assess patients, in addition to a documented review on a standardized form in patients' medical records, with no specifications for hemodialysis patients. The renal dialysis chapter of the accreditation law only requires evidence of regular consultation and coordination with other health professionals (e.g. dietitians), without further specifications of the dietitian-to-patient ratio or time. The roles and responsibilities of dietitians are thus not set nor organized by law. Accordingly, almost all hemodialysis patients in Lebanon receive only one yearly routine dietetic consultation; in addition to dietetic counseling delivered following nephrologists' consult requests.

→ *Proposed action*

Including an article in the Lebanese Healthcare Organizations Accreditation Law, specifying a minimal dietitian-to-hemodialysis patient ratio and time, as elaborated below. The article is also expected to clarify the roles and responsibilities of the dedicated dietitian. The latter could initially follow Academy of Nutrition and Dietetics (AND) and National Kidney Foundation (NKF)'s Standards of Practice (SOP) and Standards of Professional Performance (SOPP) for dietitians in nephrology nutrition [3], until country-specific standards are established (further details are provided below).

<u>Organizational considerations</u>

- *Institutional arrangement*

Currently, hospital dietitians lack institutional support, including time allocation, to deliver effective care to hemodialysis patients. 85% of Lebanese hospital dietitians spend less than ten hours at the hemodialysis unit. They can only find limited time for hemodialysis patients' consults within their other clinical, administrative and food service duties [4,5]. This limited time greatly falls below what is recommended by international guidelines [3,6–8].

→ *Proposed action*

Organizations must ensure adequate dietitian caseload (dietitian-to-patient time and ratio). This could be done through recruiting dietitians solely dedicated to hemodialysis patients, or establishing specific measurements within the hospitals' dietetic department to ensure the delivery of dietetic services compatible with the below-specified caseload. As initial implementation steps, we propose a dietitian-to-patient ratio of approximately 1:100 hemodialysis patients (not exceeding 1:150) [3]. In dialysis facilities where the dietitian will have broader responsibilities (e.g. quality improvement, development and monitoring of protocols for patient care, research), the caseload ratio should be adjusted downward. The proposed dietitian-to-patient contact time includes an initial consultation of 60-90 minutes, a follow-up within 1 month of 30-45 minutes, and regular nutritional updates of 45-60 minutes, as needed [8]. We propose this initial dietitian staffing, until the optimal dietitian-to-patient ratio of 1:70 [9] and dietitian-to-patient contact time of approximately 2 hours per month [6] could be achieved.

- *Financial arrangement*

The presence of a dedicated dietitian incurs additional costs to dialysis providers in Lebanon (hospitals); resistance of the latter bodies towards implementing this technology is expected.

→ *Proposed action*

On average, the cost of the intensive nutrition education is around $1 per patient per session, assuming an optimal dietitian-to-patient ratio of 1:70. This cost is expected to further decrease on the long-run, due to the omission of the cost of the initial training of the dietitians, representing approximately 10% of the cost of the intervention. The monthly budget implications of making a dedicated dietitian available for the patient would be on average $12.5 (approximately $40,000 for the 3,300 patients currently treated by hemodialysis in Lebanon). As found in our economic evaluation, the monthly difference in the decrease in healthcare costs between the proposed intervention and the existing practice during the post-implementation phase was $151 per patient. This amount would offset more than 10 times the cost of the nutrition intervention. As the third party payers are expected to benefit from the cost savings resulting from the implementation of this technology, the cost of the intensive nutrition education could be added to the bundled payment to the hospitals by third party payers. The latter will be in charge of reimbursing the dietitians. This reimbursement system would be similar to the mechanism adopted in the USA [10].

Provider considerations

- *Delivery arrangement 1:*

Lebanese hospital dietitians' knowledge of renal nutrition guidelines is poor, and specialized education, training or certification in renal dietetics do not exist in Lebanon [4,11].

→ *Proposed action:*

Dietitians must be provided with sufficient specialized education enabling them to deliver effective, comprehensive and individualized care using cognitive/behavioral strategies and culturally specific educational tools, along with easy-to-apply skills [12–14]. A possible roadmap to developing renal dietetic specialization in Lebanon consists of 1) integrating an intensive evidence-based renal dietetics course within the nutrition bachelor program or post-baccalaureate dietetic internship, 2) establishing a health practice accreditation system that periodically audits the knowledge and practice of dietitians working with renal patients, and 3) establishing a system of obligatory continuing education to maintain license to practice in this field [11]. Until renal dietetic specialization is ensured within the didactic or internship programs in Lebanon, providing intensive trainings to practicing dietitians intended to be allocated to hemodialysis units could be proposed, similarly to what was successfully done in the Nutrition Education for Management of Osteodystrophy (NEMO) trial [15]. Dietitians allocated to hemodialysis units would refer to international tools to assess their current skill levels and to identify areas for additional professional development in this practice area, such as the Academy of Nutrition and Dietetics (AND) and the National Kidney Foundation (NKF)'s SOP and SOPP [3], until country/regional-specific tools are elaborated.

- *Delivery arrangement 2:*

Country-specific practice-guidelines for renal dietetics do not exist in Lebanon.

→ *Proposed action*

International evidence-based practice-guidelines on renal nutrition [6,7,16,17] would be applied, until country/regional-specific standards and guidelines are established.

- *Multidisciplinary care arrangement*

Disparity in the nutrition-related perceptions and recommendations between members of nephrology care team do exist [18]. Other members of the nephrology team were shown to have limited knowledge and skills related to some aspects of the nutritional management of hemodialysis patients

[19], and overlap in patient delivered messages might be a potential source of confusion for the patient [20].

→ *Proposed action*

Dietitians are uniquely qualified to provide effective, tailored, and safe nutrition care to renal patients [21,22]. Recognizing the role of the dietitians at the hemodialysis unit, involving them in the multidisciplinary patient care, standardizing practices amongst renal care professionals, actively discouraging and correcting alienation between staff members, promoting teamwork, respect for work product among staff members, and effective communication and coordination of care between all healthcare providers [9,20,23] are best practices in the hemodialysis units, that should be implemented for optimal patient outcomes. Until shortages in qualified dedicated dietitians are bridged, task shifting, i.e. delegation of some nutrition-related tasks, where appropriate, to less specialized health workers in nutrition (e.g. nurses) could be adopted as a temporary solution.

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SUMMARY

Hyperphosphatemia is a common condition among hemodialysis patients, and is associated with increased risks of morbidity and mortality and higher health care costs. Hyperphosphatemia is typically managed through a combination of hemodialysis treatment, phosphate binding medications and dietary phosphorus restriction; this approach is supported by clinical evidence. Given budgetary constraints, information about the value for money spent on health interventions is being used increasingly by decision makers to guide the efficient allocation of available health care resources. Health technology assessment (HTA), a form of policy research that systematically examines both the direct and indirect consequences of a health technology, provides relevant input to decision making in policy and practice. Specifically, economic evaluations, a part of HTA, compares health technologies in terms of costs and outcomes to assess their value for money.

As in many countries, hemodialysis is a major public health problem in Lebanon, and hyperphosphatemia management in this patient population remains an ongoing challenge. Moreover, as part of the public rehabilitation strategy for the health sector, the integration of HTA into the decision making process for national public health care has been advocated. However, to date, no concrete action was taken in this regard. Therefore, we aim in this dissertation to provide insights into the HTA of hyperphosphatemia management among hemodialysis patients and explore economic considerations in this regard, with a focus of the Lebanese setting.

The escalating clinical and economic burden of hyperphosphatemia, coupled with the high cost of its management on one hand, and limited healthcare resources on the other, provide the rationale for fostering the search for cost-effective interventions for managing hyperphosphatemia among hemodialysis patients. In particular, we first provided an overview of the cost-effectiveness of phosphorus-lowering interventions in this patient population. We then explored the financial burden of hemodialysis and hyperphosphatemia management through phosphate binders in Lebanon. Finally, we assessed the clinical and economic value of intensive nutrition education as a phosphorus-lowering intervention among Lebanese hemodialysis patients.

In ***Chapter 2***, we conducted a systematic review of published economic evaluations of interventions aiming to manage hyperphosphatemia among hemodialysis patients; we provided a descriptive analysis and critically appraised these studies. All records included in our review addressed the comparative cost-effectiveness of phosphate binders, and we could not identify any study on different hemodialysis modalities, a low-phosphorus diet, or other types of interventions. We found limited evidence on the cost-effectiveness of non-calcium based binders in prevalent and incident patients, in first-line and sequential use. We could not generate firm conclusions due to the sub-optimal quality and heterogeneity of the included studies; moreover, there was a lack of studies addressing some clinical scenarios. In ***Chapter 3***, we explored the societal cost-of-illness of hemodialysis and its drivers in Lebanon. We also provided insights into the financial burden of managing hyperphosphatemia through phosphate binders in this patient population in Lebanon. Our estimates revealed a 6-month societal cost of hemodialysis of $9,258, with 91.7% of this cost attributable to healthcare costs, 4.2% to patient and family costs, and 4.1% to costs in other sectors (transportation), highlighting the high financial burden of hemodialysis on Lebanese society and the Lebanese healthcare system. We also observed the high cost of managing serum phosphorus through phosphate binders, especially calcium-free agents. In ***Chapter 4***, we evaluated the clinical effect of intensive nutrition education on hemodialysis patients suffering from hyperphosphatemia. We found that this intervention is superior to the existing practice in Lebanon and to another proposed alternative, in terms of increasing patients' adherence to a low-phosphorus diet and managing their hyperphosphatemia without compromising their nutritional status. Finally, in ***Chapter 5***, we explored the economic value of this nutrition education in Lebanon, using several scenarios. We found that the cost of the intensive nutrition education was very low in comparison with the societal cost of hemodialysis and the costs of other health interventions in this patient population. We also noted that this intervention yielded the greatest decrease in use of resources and societal costs in comparison with the existing practice and the other alternative. However, we could not find any effect on quality-adjusted life-years, and the intervention was dominated by its comparators. In light of the significance between group differences in baseline key parameters (serum phosphorus and malnutrition inflammation status), interpreting our findings was challenging. We suggest further long-term evaluation of intensive nutrition education on equitable groups at baseline, using a modeling study.

The findings of this dissertation present several implications for clinical practice, for decision making in the sphere of public health, and for research, notably in local HTA. First, we provide additional high-quality evidence about the beneficial clinical effect of intensive nutrition education as a phosphorus-lowering intervention among hyperphosphatemic hemodialysis patients. Second, the results of this study provide insights for public health policy makers about the debilitating financial burden of hemodialysis in Lebanon and about the need for a rational allocation of resources for hyperphosphatemia management in this patient population. We also provide some concrete implications for the implementation of national HTA. Finally, this dissertation generates several directions for future research in the field of hyperphosphatemia management among hemodialysis patients, and in the field of HTA, specifically economic evaluations, in Lebanon.

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Finally, I dedicate this thesis to the soul of my father Ghassan, to my mother Maha, to my sister Rima, to my brother Tony… and to you my God, my all…

Rana

Curriculum vitae

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Rana Rizk was born on November 10th, 1987, in Chiah, Lebanon. She obtained her bachelor of sciences in Human Nutrition and Dietetics in 2009 and her master of sciences in Human Nutrition- Option: Clinical Nutrition in 2013 from the Holy Spirit University of Kaslik, Lebanon. She obtained her master in public health in Epidemiology and Biostatistics in 2016 from the Lebanese University, Lebanon.

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